

Electronic Structure of Heterocyclic Sulfur Compounds

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I. Introduction

A. SCOPE

The objective of the present review is to give a critical and, as far as possible, synthetic survey of those problems of the chemistry of σ -bivalent sulfur that have been studied by quantum-chemical methods. For various reasons, this limitation had to be disregarded in several places; this applies above all to the compounds mentioned in Section II, E. Sulfoxides and sulfones are not included, but references

are given to papers in which models of these compounds were studied theoretically. Similarly treated are compounds containing sulfur outside the ring as well as acyclic compounds. In view of this selection it is apparent that numerous important studies of sulfur compounds have been omitted; experimental studies are mentioned only to the extent necessary for checking the validity of theoretical predictions. Special attention is paid to chemical reactivity and electronic spectra. The review contains molecular diagrams of only a few compounds which were not available in the literature at the time this manuscript was written. On the other hand, energy characteristics are summarized as completely as possible, along with the corresponding data for the parent hydrocarbons.

B. METHODS OF THEORETICAL TREATMENT

1. *A Note on Theoretical Methods*

More than 95 percent of the theoretical studies of heterocyclic sulfur compounds have been performed by the simple molecular orbital (MO) method. The basic concepts underlying this method and the course of numerical computations for models of various compounds have been described in numerous monographs,¹⁻⁴ that by Streitwieser⁴ being particularly suitable for chemists. Here it will be sufficient to remind the reader (cf. ref. 5) that the wave functions of delocalized π -molecular orbitals, ψ_i , are represented by linear combinations of atomic functions, φ_j , which describe the state of p_z atomic orbitals having a nodal plane in the plane of the σ -bond skeleton of a conjugated planar molecule and directed along the axes that pass through atom nuclei and are perpendicular to the plane of the σ -skeleton:

$$\psi_i = \sum_{j=1}^n c_{ij} \varphi_j \quad (i = 1, 2, \dots n) \quad (1)$$

¹ C. A. Coulson, "Valence." Oxford Univ. Press, London, 1952.

² R. Daudel, R. Lefebvre, and C. Moser, "Quantum Chemistry." Interscience, New York, 1959.

³ B. Pullman and A. Pullman, "Les théories électroniques de la chimie organique." Masson, Paris, 1952.

⁴ A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists." Wiley, New York, 1961.

⁵ J. H. Ridd, in "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Vol. I, p. 109. Academic Press, New York, 1963.

In Eq. (1), c_{ij} represents the expansion coefficient at the j -th atomic orbital (φ_j) in the i -th π -molecular orbital (ψ_i). The coefficients c_{ij} ($j = 1, 2, \dots n$) fully describe the wave function ψ_i ; their numerical values are obtained by solving the system of equations (2).

$$\sum_{j=1}^n (H_{jk} - S_{jk} E) c_{ij} = 0 \quad (i = 1, 2, \dots n) \quad (2)$$

In the simple version of the MO LCAO (linear combination of atomic orbitals) theory, the quantities H_{jk} and S_{jk} , defined by Eqs. (3–5), are treated as empirical parameters, thus there is no need for detailed information concerning the character of the atomic functions φ_j .

$$H_{jk} = \beta_{jk} = \int \varphi_j \mathbf{H}' \varphi_k d\tau \quad (\text{resonance integral}) \quad (3)$$

$$H_{jj} = \alpha_j = \int \varphi_j \mathbf{H}' \varphi_j d\tau \quad (\text{Coulomb integral}) \quad (4)$$

$$S_{jk} = \int \varphi_j \varphi_k d\tau \quad (\text{overlap integral}) \quad (5)$$

In Eqs. (3) and (4), \mathbf{H}' stands for the effective one-electron Hamiltonian; the integration is over the whole space. In the simple method, a number of simplifying assumptions about the values of the integrals β_{jk} , α_j , and S_{jk} are introduced; in the case of molecules containing no heteroatoms these are known as the Hückel approximations. It seems useful to use this designation also for molecules with heteroatoms, and in the present review this method will be referred to as the Hückel molecular orbital (HMO) method according to Streitwieser's suggestion.⁴

Physically meaningful solutions of the system of equations (2) are obtained only for certain values of molecular orbital energies, E_i , which follow from the determinantal equation

$$|H_{jk} - S_{jk} E| = 0 \quad (6)$$

It only remains to be added that the Coulomb integral of the carbon $2p_z$ orbital (α_C) is conventionally set equal to zero (the origin of the energy scale in the HMO method) and that the resonance integral of the C—C π -bond (β_{CC}) is equal to one (the energy unit in the HMO method). The values of Coulomb integrals of p_z orbitals of heteroatoms are in general different from α_C and are usually given in the form (for a $2p_z$ orbital of atom X):

$$\alpha_X = \alpha_C + \delta_X \beta_{CC}, \quad (7)$$

where constant δ_X , roughly speaking, is a measure of the electro-negativity of the relevant orbital. In a similar way, resonance integrals of π -bonds other than C—C are usually given in β_{CC} units. For a C—X π -bond:

$$\beta_{CX} = \rho_{CX} \beta_{CC}, \quad (8)$$

where ρ_{CX} is a constant roughly expressing the strength of the π -bond.

As an example, starting assumptions and the result of an HMO treatment of a model of the thiophene molecule are presented:



Starting assumptions:

$$\alpha_S = \alpha_C + 0.5\beta_{CC}; \quad \alpha_{C_1} = \alpha_{C_2} = \alpha_{C_3} = \alpha_{C_4} = \alpha_C$$

$$\beta_{CS} = 0.6\beta_{CC}; \quad \beta_{C_1C_2} = \beta_{C_2C_3} = \beta_{C_3C_4} = \beta_{CC}$$

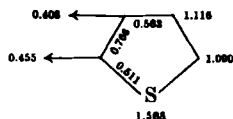
$$S_{ij} = 0 (i \neq j); \quad S_{jj} = 1.$$

Solving a determinantal equation of the type (6) (orbital energies) and systems of equations of the type (2) (expansion coefficients) gives the results shown in the following tabulation.

i	E_i	ψ_i
1	$\alpha_C + 1.8013\beta_{CC}$	$0.3776\varphi_1 + 0.4094\varphi_2 + 0.5110\varphi_3 + 0.5110\varphi_4 + 0.4094\varphi_5$
2	$\alpha_C + 0.6860\beta_{CC}$	$0.8070\varphi_1 + 0.1251\varphi_2 - 0.3984\varphi_3 - 0.3984\varphi_4 + 0.1251\varphi_5$
3	$\alpha_C + 0.6180\beta_{CC}$	$0.6015\varphi_2 + 0.3718\varphi_3 - 0.3718\varphi_4 - 0.6015\varphi_5$
4	$\alpha_C - 0.9873\beta_{CC}$	$-0.4541\varphi_1 + 0.5628\varphi_2 - 0.2832\varphi_3 - 0.2832\varphi_4 + 0.5628\varphi_5$
5	$\alpha_C - 1.6180\beta_{CC}$	$0.3718\varphi_2 - 0.6015\varphi_3 + 0.6015\varphi_4 - 0.3718\varphi_5$

Within the HMO framework, simple arithmetic leads from the values of orbital energies to the values of total π -electronic energy (W), delocalization energy (DE), excitation energy of the $N \rightarrow V_1$ transition [$E(N \rightarrow V_1)$], and other quantities.¹⁻⁴ In our case, these values are: $W = 6\alpha_C + 6.2107\beta_{CC}$; $DE = 1.2107\beta_{CC}$; and $E(N \rightarrow V_1) = 1.6053\beta_{CC}$. It is a frequent practice to lead discussions in terms of the factors k_i which appear in the expressions for orbital energies, $E_i = \alpha_C + k_i\beta_{CC}$.

The sum of all these factors for a specific problem is equal to the trace of the matrix of the corresponding characteristic problem⁴; the sum of their squares equals the sum of the squares of all matrix elements of the corresponding characteristic problem.^{5a} These relations are useful for checking the values of orbital energies. By an equally simple procedure¹⁻⁴ the values of expansion coefficients yield the values of π -electron densities (q), bond orders (p), and free valences (F); these quantities are usually presented in the form of a molecular diagram:



Somewhat more involved is the computation of further reactivity indices: Wheland's atom localization energy, A^6 ; exact superdelocalizability, S^7 ; various polarizabilities, π^8 ; Brown's factor, Z^9 ; Dewar's reactivity number, A_D^{10} and the approximate superdelocalizability, S'^7 .

The values of q , p ,¹¹ and S may be checked by use of the relations shown in Eqs. (9-11).

$$\sum_{j=1}^m q_j = l \quad (9)$$

$$W = \sum_{j=1}^m q_j \alpha_j + 2 \sum_{k < j} p_{kj} \beta_{kj} \quad (10)$$

$$\sum_{j=1}^m S_{j,e} = 2 \sum_{i=1}^n 1/k_i \quad (11)$$

In Eqs. (9-11), l means the total number of π -electrons in the molecule, m is the total number of orbitals in conjugation, n is the number of

^{5a} J. Koutecký, J. Čížek, and J. Paldus, personal communication (1960).

⁶ G. W. Wheland, *J. Am. Chem. Soc.* **64**, 900 (1942).

⁷ K. Fukui, T. Yonezawa, and C. Nagata, *Bull. Chem. Soc. Japan* **27**, 423 (1954).

⁸ C. A. Coulson and H. C. Longuet-Higgins, *Proc. Roy. Soc. (London)* **192A**, 16 (1947).

⁹ R. D. Brown, *J. Chem. Soc.* 2232 (1959).

¹⁰ M. J. S. Dewar, *J. Am. Chem. Soc.* **74**, 3357 (1952).

¹¹ C. A. Coulson and H. C. Longuet-Higgins, *Proc. Roy. Soc. (London)* **191A**, 39 (1947).

occupied π -molecular orbitals, k and j are the indices of atomic orbitals (positions), and the subscript e means electrophilic substitution; similar relations hold for $S_{j,n}$ and $S_{j,r}$ (n means nucleophilic and r radical substitution).

2. Models of Sulfur Atom Orbitals

In its ground state, the sulfur atom has the electron configuration $(1s)^2 (2s)^2 (2p_x)^2 (2p_y)^2 (2p_z)^2 (3s)^2 (3p)^4$ and, in addition, disposes of five $3d$ orbitals exploitable for bonding. We shall restrict our further considerations to the $3s$, $3p$, and $3d$ orbitals, which are important for the bonding capability of sulfur. With conjugated heterocyclic compounds containing σ -bivalent sulfur, one can imagine, in the simplest

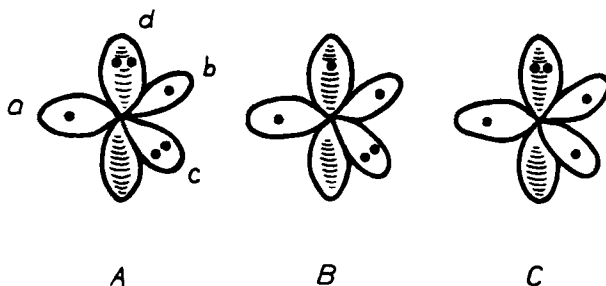


FIG. 1. Occupancy of the $3sp^2$ (a, b, c) and $3p_z$ (d) sulfur orbitals by electrons in various types of conjugated compounds. In cases A and B, c is a non-bonding atomic orbital (the orbitals are somewhat deformed for the sake of clarity).

approach, that three hybrid $3sp^2$ orbitals arise by combination of the $3s$, $3p_x$, and $3p_y$ orbitals, two of them being occupied by one electron and forming the C—S σ -bonds by overlap with carbon sp^2 orbitals while the third one, occupied by two electrons, is a non-bonding atomic orbital (Fig. 1A). The $3p_z$ orbital, occupied by two electrons, overlaps with neighboring p_z orbitals and participates in the formation of delocalized π -molecular orbitals. This model may be adopted when studying the electronic structure of compounds like thiophene (its most serious deficiency, in this case, being the fact that its hybrid $3sp^2$ orbitals lie at an angle of 120° while it is well known that the C—S—C angle in thiophene is only 91°) as well as of those of the thiapyrylium or cyclothiolium types (see Section II, E). With these systems, the positive charge results from the removal of one electron from the atomic orbitals when forming the molecule. In the case of thiapyrylium

the electron has been removed from the $3p_z$ orbital (Fig. 1B) and the resultant positive charge is therefore delocalized; on the other hand, in the case of σ -tervalent sulfur the electron has been removed from the non-bonding atomic orbital, hence the positive charge is localized at the sulfur atom (Fig. 1C).

Although d -orbital participation in the bonding of sulfur in conjugated compounds was first considered as early as 1939 by Schomaker

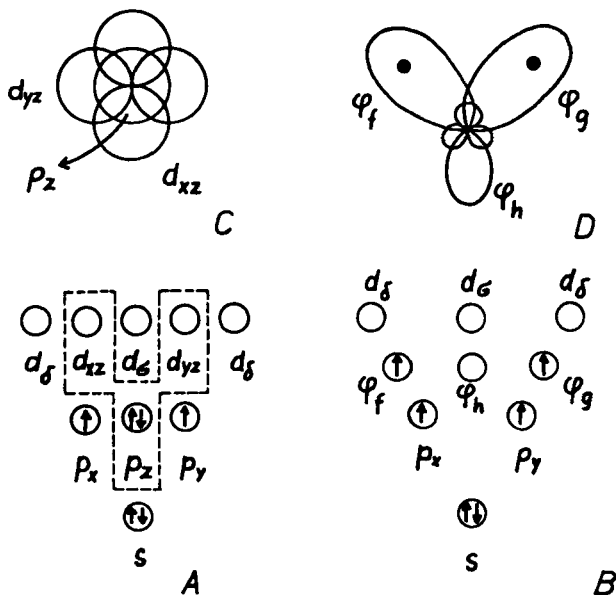


FIG. 2. Schematic representation of the formation of hybrid $3pd^2$ orbitals (B, D) from atomic orbitals (A, C). Figures A and B are taken from a paper by Metzger and Ruffler,¹⁴ C and D from one by Longuet-Higgins.¹³

and Pauling,¹² it was not until 1949 that Longuet-Higgins¹³ formulated the problem in terms of the MO theory. He studied the properties of orbitals resulting from hybridization of $3p$ and $3d$ orbitals, his starting point being the analogy between thiophene and benzene. According to Longuet-Higgins, the $2p_z$ atomic orbitals of carbon atoms adjacent to the sulfur atom are labeled ϕ_a and ϕ_b ; the $3p_z$, $3d_{yz}$, and $3d_{xz}$ orbitals of the sulfur atom are designated ϕ_c , ϕ_d , and ϕ_e , respectively. By linear

¹² V. Schomaker and L. Pauling, *J. Am. Chem. Soc.* **61**, 1769 (1939).

¹³ H. C. Longuet-Higgins, *Trans. Faraday Soc.* **45**, 173 (1949).

¹⁴ J. Metzger and F. Ruffler, *J. Chim. Phys.* **51**, 52 (1954).

combination of the φ_c , φ_d , and φ_e orbitals, hybrid $3pd^2$ orbitals, φ_f , φ_g , and φ_h (Fig. 2), are introduced:

$$\varphi_x = \frac{S_{ac}S_{ae}\varphi_c + S_{ad}S_{ae}\varphi_d \pm (S_{ac}^2 + S_{ad}^2)\varphi_e}{[(S_{ac}^2 + S_{ad}^2)(S_{ac}^2 + S_{ad}^2 + S_{ae}^2)]^{1/2}} \quad (12)$$

In Eq. (12), the plus sign holds for $x = f$ and the minus sign for $x = g$.

$$\varphi_h = \frac{S_{ad}\varphi_c - S_{ac}\varphi_d}{(S_{ac}^2 + S_{ad}^2)^{1/2}} \quad (13)$$

In Eqs. (12) and (13), S_{ij} is the overlap integral between the i -th and j -th orbital. The shape of the φ_f , φ_h , and φ_g orbitals is apparent from

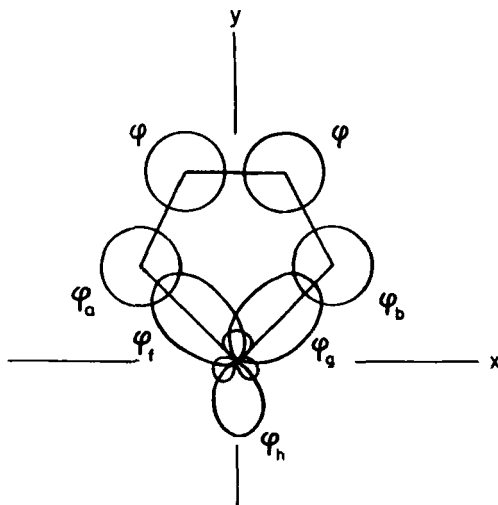


FIG. 3. Model of the atomic orbitals in thiophene (according to Longuet-Higgins¹³); φ 's indicate carbon $2p_z$ orbitals.

Fig. 2. The φ_h orbital does not interact with other atomic orbitals; for the sake of numerical calculations within the HMO framework, the φ_f and φ_g orbitals may simply be replaced by carbon $2p_z$ orbitals. The model of thiophene is presented in Fig. 3; the x and y axes are shown, the z -axis is perpendicular to the plane of the molecule.

Although this model is very attractive from the chemist's point of view, clearly reflecting analogies such as those between thiophene and

benzene, thiazole and pyridine, thialene and azulene, thiapyrylium and tropylium, which led to its rather frequent use, in the course of time some deficiencies have become apparent.

3. *The Empirical Parameters of the HMO Method*

This section presents a summary of data on the most frequently adopted values of HMO empirical parameters used in the study of sulfur compounds.¹⁵⁻¹⁷ Overlap between neighboring orbitals has been neglected in most of the calculations. The values of Coulomb and resonance integrals are given in terms of the constants δ_i and ρ_{ij} defined by Eqs. (7) and (8). Models considering *d*-orbital participation (due to Longuet-Higgins¹³) shall be called Models A: the accompanying number specifies the values of the constants used (Table I). Model B

TABLE I
EMPIRICAL PARAMETERS, MODEL A

	$\delta_i (= \delta_p)$	ρ_{1p}	$\rho_{1a} (= \rho_{pb})$
A 1	0	1	0.6
A 2	0	1	0.8
A 3	(0, -1 >)	1	0.6-0.8

shall mean a model that does not consider *d*-orbital participation (Table II).

The δ and ρ values that are not given in the survey have the standard values of $\delta = 0$ and $\rho = 1$. In the case of compounds containing two sulfur atoms and/or other heteroatoms, the values given in Table III have also been used frequently. For the sake of brevity, we shall call this set of parameters Model C. It is easily seen that some of these values are not fully adequate, especially the parameters for oxygen.

¹⁵ R. Zahradník and J. Koutecký, *Collection Czech. Chem. Commun.* **28**, 1117 (1963).

¹⁶ R. Zahradník and C. Párkányi, *Collection Czech. Chem. Commun.* **30**, 195 (1965) (thiophenes) and *Collection Czech. Chem. Commun.*, in press (analogues of non-alternant hydrocarbons).

¹⁷ R. Zahradník, C. Párkányi, V. Horák, and J. Koutecký, *Collection Czech. Chem. Commun.* **28**, 776 (1963).

It has been found many times, however, that this circumstance is irrelevant to qualitative reasoning. Moreover, it does not disturb quantitative correlations, e.g. of spectral data, provided that the set of

TABLE II
EMPIRICAL PARAMETERS, MODEL B

	δ_s	$\delta_{C(s)}$	ρ_{CS}
B 1	1	0.1	0.6
B 2	1	0	0.6
B 3	1	0.1	0.8

TABLE III
EMPIRICAL PARAMETERS, MODEL C

Atom	δ_i	Bond	ρ_{ij}
N, endocyclic (as in pyridine)	0.5	C-N S-N	1.0 0.6
N, nitrile	0.5	C=N	1.4
N, exocyclic	1.0	C-N	1.0
O, endocyclic	2.0	C-O	$\sqrt{2}$
O, exocyclic	2.0	C-O	$\sqrt{2}$
S	— ^a	S-S C-S	0.5 — ^a
Cl	2.0	C-Cl	0.4

^a Cf. Tables I and II.

compounds studied is sufficiently large. In the cases where other values of the parameters have been used, the relevant data are to be found at the corresponding place in the text.

C. SOME GENERAL REMARKS

During recent years it has become apparent that the HMO method is suitable not only for qualitative but—in a certain sense—also for quantitative studies of organic compounds. It should be realized, however, that it is only possible to obtain correct *relative* values of certain quantities. The reasonability of the conclusions reached by the theory is therefore best checked by examining the closeness of the

correlation between a sufficiently extensive set of experimental data and a series of corresponding theoretical quantities. If the correlation proves fairly close, it may be concluded that the physical model as well as the mathematical approximation are adequate. Now, the empirical relation thus obtained can, of course, be used for interpolations. As for the correlation itself, two facts must be kept in mind. In general, the regression lines need not go through the origin, and data for compounds of different structural types usually lie on separate straight lines. It further seems worth mentioning that the choice of HMO empirical parameters is a problem of secondary importance if a large set of structurally related compounds is studied.

The considerable arbitrariness in the nomenclature of organic compounds is somewhat puzzling. Moreover, none of the systems used is fully consistent and free of rather awkward names. The nomenclature used in this review is necessarily subject to these shortcomings; the rules given in the Second Edition of "The Ring Index" have been respected as far as possible. A note on the writing of structural formulas is included in Section I, D. The symbols α and β are used for α_C and β_{CC} , respectively. For the sake of brevity, expressions such as tropylia, dithiolia, etc. are used instead of tropylium ions, dithiolium ions, etc. in this review.

The reader's attention should be drawn to a recent review devoted to expansion of the sulfur outer shell.^{17a}

D. CLASSIFICATION OF COMPOUNDS STUDIED

To classify a conjugated heterocyclic sulfur compound containing one or more σ -bivalent sulfur atoms, all carbocyclic rings (usually benzene rings) attached to the heterocyclic system by one side only are disregarded (all compounds which yield the same parent skeleton by this procedure are further taken for benzo derivatives of this parent skeleton). In accordance with the Longuet-Higgins model, a $-\text{CH}=\text{CH}-$ group is then substituted for each sulfur atom and the isocyclic skeleton obtained is classified according to the number of rings and of carbon atoms in the rings (alternant and non-alternant) as follows¹⁸:

^{17a} G. Cilento, *Chem. Rev.* **60**, 147 (1960).

¹⁸ In principle, recently published¹⁹ rules for writing structural formulas have been adhered to in the present review with the one exception that a full circle in the cycle is used to denote not only a π -electron sextet but any number of π -electrons consistent with the Hückel rule in general.

¹⁹ W. Baker, *Proc. Chem. Soc. (London)* 75 (1959).

1. Monocyclic (Section II, A)

a. Alternant (Section II, A, 1)



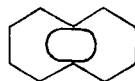
(1)



(2)



(3)



(4)

b. Non-alternant²⁰ (Section II, A, 2)

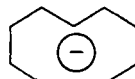
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(6)



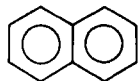
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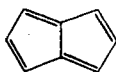
(8)

2. Bicyclic (Section II, B)

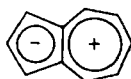
a. Alternant (Section II, B, 1)

(9)²¹

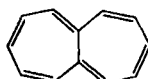
b. Non-alternant (Section II, B, 2)



(10)



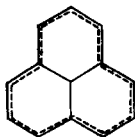
(11)



(12)

3. Tricyclic (Section II, C)

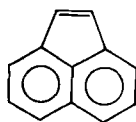
a. Alternant (Section II, C, 1)



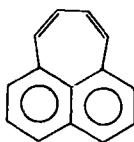
(13)

²⁰ Forms obeying the Hückel rule are given.²¹ According to the present rules of classification, thiophthene is an analogue of naphthalene; benzo[b]thiophene, however, belongs to the benzo derivatives of analogues of benzene.

b. Non-alternant (Section II,C,2)



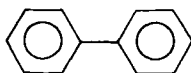
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(15)

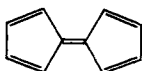
4. Diphenyl- and fulvalene-like (Section II, D)

a. Alternant (Section II, D, 1)

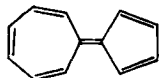


(16)

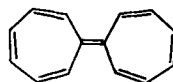
b. Non-alternant (Section II,D,2)



(17)



(18)

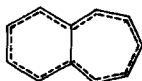


(19)

Compounds with σ -tervalent sulfur atoms are considered as a special group in Section II, E; the parent skeleton is derived by substituting the sulfur atoms with tertiary carbon atoms.



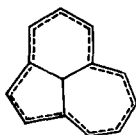
(20)



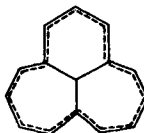
(21)



(22)



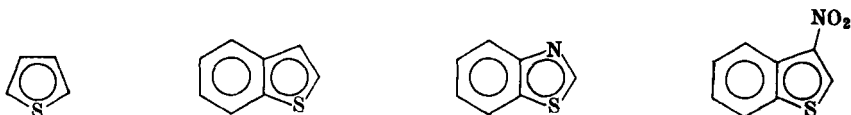
(23)



(24)

Miscellaneous other compounds are dealt with in Sections II, F and II, G.

As already stated, benzo derivatives obtained by fusing a benzenoid system to one side of the parent skeleton do not represent a separate group, nor do derivatives and hetero analogues (derived mostly by replacing a secondary sp^2 carbon atom by a sp^2 nitrogen atom). Thus, e.g., the following compounds belong in Group 1:



Various sulfur compounds are considered in the order indicated in Section II.

II. Electronic Structure, Reactivity, and some Physical Properties

A. ANALOGUES OF MONOCYCLIC HYDROCARBONS

1. Parent Skeleton: An Alternant Hydrocarbon

a. *Analogues of Cyclobutadiene* (1). Thiirene (**25**) has not yet been prepared; HMO calculations^{22, 23} suggest that it will be very unstable



(both Models A and B predict zero delocalization energy) and that it would exhibit an absorption maximum in the near-UV region. The saturated analogue, thiacyclopropane,²⁴ has an absorption maximum at 260 m μ .

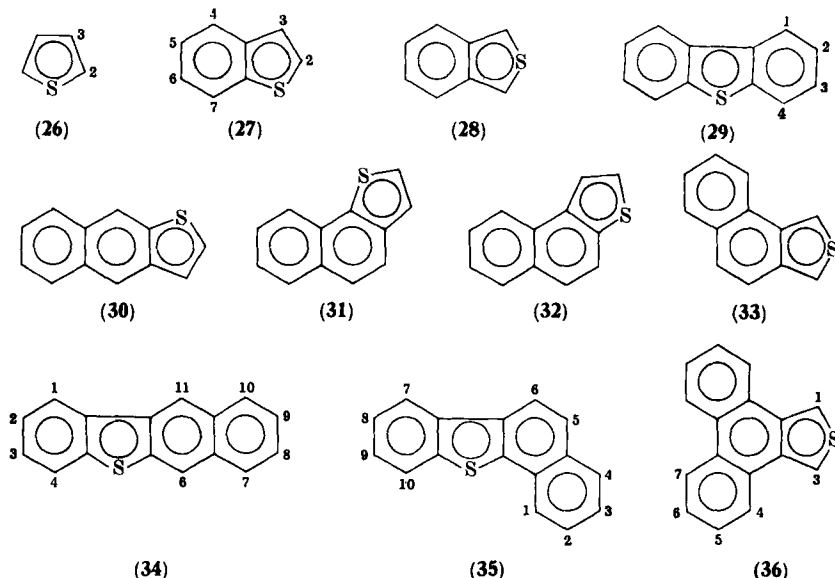
b. *Analogues of Benzene* (2). Thiophene (**26**) is probably the most practically important of the sulfur heterocyclic compounds. The chem-

²² All HMO calculations for three- and four-membered rings can be considered at best only roughly informative because with these substances one of the assumptions of the HMO method is not fulfilled, namely negligible σ - π interaction.

²³ R. Zahradník, unpublished results (1963).

²⁴ R. E. Davis, *J. Org. Chem.* **23**, 216 (1958).

istry of this compound and its derivatives has been thoroughly reviewed.²⁵⁻²⁸ Numerous benzo derivatives of thiophene (27-36) have been synthesized and studied theoretically.



The first quantum chemical study of thiophene was due to Wheland and Pauling²⁹ who used a model neglecting *d*-orbital participation and demonstrated that the inductive effect must be allowed for in order to explain its chemical reactivity. Valence-bond¹²(VB) (cf. ref. 29a) and free-electron (FE) treatments³⁰ followed. A novel approach was devised by Longuet-Higgins¹³ who studied a model in which the

²⁵ F. F. Blicke, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 1. Wiley, New York, 1950.

²⁶ D. K. Fukushima, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 2. Wiley, New York, 1951.

²⁷ H. D. Hartough, F. P. Hochgesang, and F. F. Blicke, in "Thiophene and Its Derivatives" (A. Weissberger, ed.), Vol. 3. Interscience, New York, 1952; H. D. Hartough and S. L. Meisel, in "Compounds with Condensed Thiophene Rings" (A. Weissberger, ed.), Vol. 7. Interscience, New York, 1954.

²⁸ S. Gronowitz, *Advan. Heterocyclic Chem.* **1**, 85 (1963).

²⁹ G. W. Wheland and L. Pauling, *J. Am. Chem. Soc.* **57**, 2086 (1935).

^{29a} A. Mangini and C. Zauli, *J. Chem. Soc.* 2210 (1960).

³⁰ T. N. Rekasheva, *Opt. i Spektroskopiya* **11**, 284 (1961).

two hybrid $3pd^2$ orbitals belonging to the sulfur atom take part in the conjugation. Thiophene,^{14, 31-39} benzo[*b*]thiophene,³⁴ benzo[*c*]thiophene,³² and dibenzothiophene^{34, 40} have been studied in terms of this model. A satisfactory interpretation of the course of electrophilic substitution reactions of these molecules can be obtained from π -electron densities based on Model B or a modified Model A (A3). With benzo derivatives of thiophene, the original version of Model A fails to account satisfactorily for the reactivity data. Kikuchi³⁴ has shown that this deficiency of Model A may be removed by setting the sulfur atom orbitals more electropositive than the carbon $2p_z$ orbitals by an arbitrarily small amount (Model A3). Suitable values of δ for the *f* and *g* orbitals lie in the interval $(0, -1 >)$. Further, thiophene has been studied thoroughly⁴¹ by the method of Pariser and Parr.⁴² Models of thiophene, benzo[*b*]thiophene, and dibenzothiophene without *d*-orbital participation have also been investigated.⁴³ A quantitative study of electrophilic nitration of **27**, **29**, and diphenyl sulfide by nitric acid in acetic anhydride has been reported.¹⁷ The course of these, as well as of other substitution reactions, has been explained satisfactorily in terms of π -electron densities (for a summary, see ref. 17). Synthesis of benzo[*c*]thiophene (**28**) has succeeded only recently,^{44, 45} its instability being due to the presence of an *ortho*-benzoquinodimethane structure in the molecule; an HMO treatment yields a lower *DE* value than it does for the isomeric benzo[*b*]thiophene.¹⁷ Besides the low value of the specific *DE*, the high values of the free valence in positions 1 and 3 add to the instability of this compound. Maleic an-

³¹ G. De Alti and G. Milazzo, *Univ. Studi Trieste, Fac. Sci. Ist. Chim.* No. 24 (1958).

³² J. de Heer, *J. Am. Chem. Soc.* **76**, 4802 (1954).

³³ K. Kikuchi, *Sci. Rept. Res. Inst. Tohoku Univ.* I, **40**, 133 (1956).

³⁴ K. Kikuchi, *Sci. Rept. Res. Inst. Tohoku Univ.* I, **41**, 35 (1957).

³⁵ K. Maeda, *Sci. Rept. Res. Inst. Tohoku Univ.* I, **43**, 203 (1959).

³⁶ K. Maeda, *Bull. Chem. Soc. Japan* **33**, 304 (1960).

³⁷ L. Melander, *Arkiv. Kemi* **8**, 361 (1955).

³⁸ G. Milazzo and G. De Alti, *Gazz. Chim. Ital.* **89**, 2479 (1959).

³⁹ F. L. Pilar and J. R. Morris, *J. Chem. Phys.* **34**, 389 (1961).

⁴⁰ J. Koutecký, R. Zahradník, and J. Paldus, *J. Chim. Phys.* **56**, 455 (1959).

⁴¹ D. S. Sappenfield and M. Kreevoy, *Tetrahedron* **19**, Suppl. 2, 157 (1963).

⁴² R. Pariser and R. G. Parr, *J. Chem. Phys.* **21**, 466 (1953).

⁴³ G. Berthier and B. Pullman, *Compt. Rend.* **231**, 774 (1950).

⁴⁴ R. Mayer, H. Kleinert, S. Richter, and K. Gewald, *Angew. Chem.* **74**, 118 (1962).

⁴⁵ R. Mayer, H. Kleinert, S. Richter, and K. Gewald, *J. Prakt. Chem.* **20**, 244 (1963).

hydride adds readily at these positions. Recently, the course of radical phenylation of dibenzothiophene (29) was examined thoroughly⁴⁶ and the following reactivity order found: $1 \sim 4 > 3 > 2$. The sterically less favorable positions 1 and 4 are much more reactive than the others, which is in good agreement⁴⁶ with the values of the free valence reported in previous studies of dibenzothiophene.^{40, 43} However, the correct reactivity order for positions 2 and 3 has only recently been obtained.¹⁷

An analysis of the ESR spectrum of the dibenzothiophene radical anion^{46a} yields the following hfs (hyperfine splitting) constants ($g\sigma_{\text{HSS}}$): 5.16, 4.48, 1.46, and 0.86. The theoretical values based on HMO data for Model A2 are considerably smaller: 2.84, 2.48, 1.47, and 0.27, respectively, which led the authors to make spin-density calculations by the Hartree-Fock method. Quite recently, the spin densities have been calculated for Model B ($\delta_s = 1$, $\rho_{\text{CS}} = 0.566$),^{46b} and the following constants were obtained: 5.03, 3.99, 0.75, and -1.23 . A study of the ESR spectrum of the radical derived from 2,8-dimethyldibenzothiophene permitted the assignment of the lowest hfs constant value to the proton in position 2. In contrast to the dithiins, experimental data for dibenzothiophene radicals are better reproduced by Model B.

Reactivity indices have been calculated for a series of benzo derivatives of thiophene (see Section VI, B); the course of substitution reactions of compounds 30–36 has not yet been investigated in detail. Calculations for models of these substances yield such different q , F , and S values that the positions of maximum reactivity can be easily predicted. Figure 4 shows that the radical reactivity indices given in Section VI, B (F and S_r) are correlated. If due respect is paid to the distribution of positions into classes⁴⁷ of the benzene (class 0), α -naphthalene (class 1), and meso-anthracene (class 2) types, the correlation between F and S_r is close. However, positions adjacent to the heteroatom constitute an independent sub-group, in agreement with a similar finding in the case of pyridine-like heterocycles^{48, 49} (see also

⁴⁶ E. B. McCall, A. I. Neale, and T. J. Rawlings, *J. Chem. Soc.* 5288 (1962).

^{46a} R. Gerdil and E. A. C. Lucken, *Proc. Chem. Soc. (London)* 144 (1963).

^{46b} R. Gerdil and E. A. C. Lucken, *J. Am. Chem. Soc.* **87**, 213 (1965).

⁴⁷ J. Koutecký, R. Zahradník, and J. Čížek, *Trans. Faraday Soc.* **57**, 169 (1961).

⁴⁸ See article by R. Zahradník and J. Koutecký, p. 99.

⁴⁹ R. Zahradník and C. Párkányi, *Collection Czech. Chem. Commun.* **30**, 353 (1965).

refs. 4 and 50). This fact must be kept in mind when comparing the theoretical indices with the reactivity order of the individual positions.

The chemistry of analogues and various derivatives of the compounds discussed is quite a rich field. Thiazoles, methylthiazoles, thiadiazoles, and benzothiazoles have been studied theoretically. The agreement of theoretical indices with the course of substitution reactions and some physico-chemical properties is satisfactory (1,2-thiazole,⁵¹ 1,3-thiazole,⁵²⁻⁵⁶ thiadiazoles,⁵⁶ benzo-1,3-thiazole^{53, 54}).

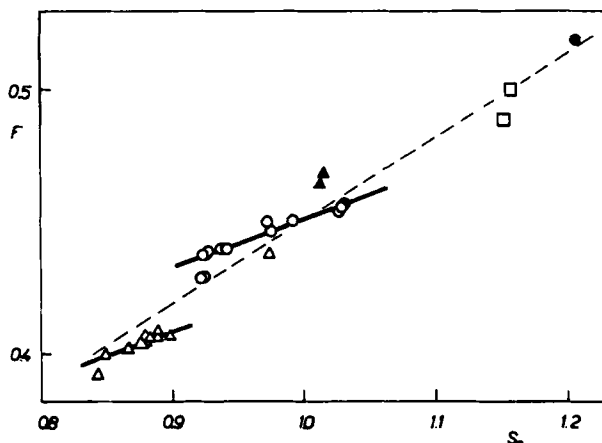


FIG. 4. Free valence plotted against radical superdelocalizability for a group of benzo derivatives of thiophene (Model B2). Designation (class): Δ (0), \circ (1), \square (2). Positions adjacent to a heteroatom are designated by solid symbols.

Parallelism between F and A_r and between q and A_n as well as A_e has been found for models of the thiadiazole and 1,3-thiazole molecules (Model A).⁵⁶

Experimental data for 2- and 3-nitrothiophenes are satisfactorily

⁵⁰ R. D. Brown in "Current Trends in Heterocyclic Chemistry" (A. Albert, ed.) p. 13. Butterworths, London, 1958.

⁵¹ A. Adams and R. Slack, *J. Chem. Soc.* 3061 (1959).

⁵² J. Metzger and A. Pullman, *Compt Rend.* **226**, 1613 (1948).

⁵³ J. Metzger and A. Pullman, *Bull. Soc. Chim. France* 1166 (1948).

⁵⁴ A. Pullman and J. Metzger, *Bull. Soc. Chim. France* 1021 (1948).

⁵⁵ E. Vincent and J. Metzger, *Bull. Soc. Chim. France* 2039 (1962).

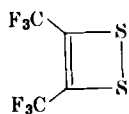
⁵⁶ R. Zahradník and J. Koutecký, *Collection Czech. Chem. Commun.* **26**, 156 (1961).

accounted for by the values of localization energies while π -electron densities lead to incorrect predictions.^{57, 58}

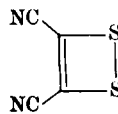
Formal substitution of two benzene double bonds by sulfur atoms leads to the four-membered heterocycle 1,2-dithiete (37). This compound has not been synthesized, although derivative 38 is known,^{59, 60} and dicyano-1,2-dithiete (39) is very probably an intermediate in some reactions of thiacyanocarbons (see below). Models of both compounds have been studied theoretically,^{23, 61} but the calculations are



(37)

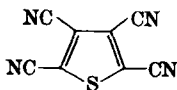


(38)

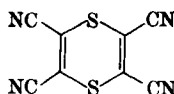


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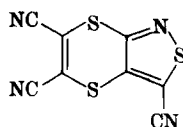
of rather limited value in view of the presence of the four-membered ring.²² In this connection a group of compounds with an unusually interesting chemistry, the thiacyanocarbons,⁶¹⁻⁶⁴ seems worth mentioning (see also refs. 65-67). In our classification these compounds are of different types, but, nevertheless, it seems desirable to discuss them together in view of their chemical interrelations. Examples of the compounds in question are 40-42⁶⁴ and 43.²³



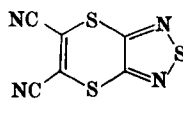
(40)



(41)



(42)



(43)

⁵⁷ L. Melander, *Acta Chem. Scand.* **9**, 1400 (1955).

⁵⁸ L. Melander, *Arkiv Kemi* **11**, 397 (1957).

⁵⁹ C. G. Krespan, *J. Am. Chem. Soc.* **83**, 3434 (1961).

⁶⁰ C. G. Krespan, B. C. McKusick, and T. L. Cairns, *J. Am. Chem. Soc.* **82**, 1515 (1960).

⁶¹ H. E. Simmons, D. C. Blomstrom, and R. D. Vest, *J. Am. Chem. Soc.* **84**, 4782 (1962).

⁶² H. E. Simmons, D. C. Blomstrom, and R. D. Vest, *J. Am. Chem. Soc.* **84**, 4756 (1962).

⁶³ H. E. Simmons, D. C. Blomstrom, and R. D. Vest, *J. Am. Chem. Soc.* **84**, 4772 (1962).

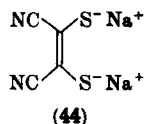
⁶⁴ H. E. Simmons, R. D. Vest, D. C. Blomstrom, J. R. Roland, and T. L. Cairns, *J. Am. Chem. Soc.* **84**, 4746 (1962).

⁶⁵ G. Bähr, *Angew. Chem.* **68**, 525 (1956).

⁶⁶ G. Bähr and G. Schleitzer, *Chem. Ber.* **88**, 1771 (1955).

⁶⁷ G. Bähr and G. Schleitzer, *Chem. Ber.* **90**, 438 (1957).

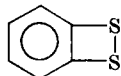
Models of compounds **40**, **41**, and **43** have been studied theoretically²³ assuming complete planarity. Disodium dimercaptomaleonitrile (**44**)⁶⁵ is a suitable starting material for the synthesis of compounds



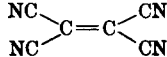
40–42. More specifically, its oxidation leads to **41** which upon heating yields **40**. The reaction of sulfur with **41** in the presence of nucleophilic reagents results in the formation of **42**. The infrared spectra of compounds **40–42** are very simple. All these compounds behave as π -acids. In this regard they resemble quinones rather than tetracyanoethylene⁶⁴ which ranks among the strongest π -acids. Some qualitative information may be gained by inspection of Fig. 5 which presents the energies of the highest occupied and lowest free π -molecular orbitals for a few of the compounds discussed. In addition, it includes data for compounds **45** and **46** and, for the sake of comparison, data for tetracyanoethylene (**47**) and tetracyanoparaquinodimethane



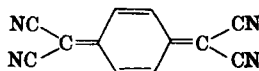
(45)



(46)



(47)

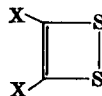


(48)

(48). Compound **41** can be expected to be the strongest π -acid of the compounds **40**, **41**, and **43**. It has been found⁶⁴ that **41** is considerably more easily reduced polarographically than **40**, and it is worth noting that the energy of the LFMO (lowest free π -molecular orbital) of the model of compound **41** is substantially lower than that of **40** (Fig. 5). Much attention has been paid⁶¹ to the electronic structure of **44**, and models of **49** and **50** have been studied by the HMO method. In structural formulas **49** and **50**, X represents $(\text{CH}_3)_2\text{N}$, CH_3 , CF_3 , and CN .



(49)



(50)

The values of orbital energies and molecular diagrams are given in ref. 61. Quite interesting is the finding that electron-withdrawing substituents such as CF_3 strongly stabilize the cyclic form **50**.

c. *Analogues of Cyclooctatetraene* (3). While thiepin (51) and unsubstituted benzothiepins have so far resisted synthesis,⁶⁸ dibenzothiepin (52) is a stable compound.^{69, 70} The probable reason for the

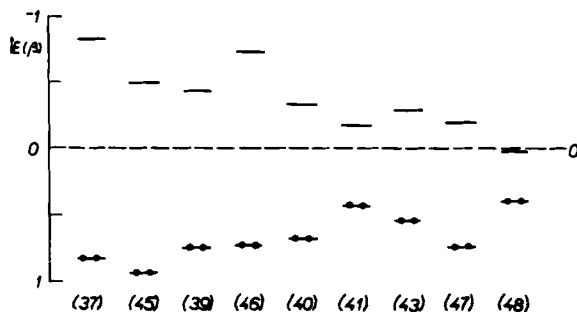
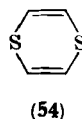
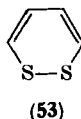
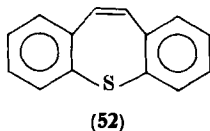
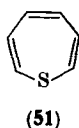


FIG. 5. HOMO and LFMO energies (parameters A 1, C).¹⁶

instability of thiepin and analogous substances is the presence of eight π -electrons, which makes the highest occupied molecular orbital contribute unfavorably to the total π -electronic energy.⁴



Formal replacement of one double bond in thiepin (51) by a sulfur atom leads to 1,2- (53) and 1,4-dithiin (54). The latter compound has been synthesized,^{70a} and it is a non-planar, thermally stable molecule with a reactivity widely different from that of aromatic systems. A refined HMO method (Model B)⁷¹ has been used successfully to explain known properties of 54, and remarkably good agreement was obtained between the calculated and experimental C—S—C and C—C—S bond angles. For the parameters used ($\delta_s = 0$, $\rho_{CC} = 1.06$, $\rho_{CS} = 0.77$), the highest occupied orbital is anti-bonding, in agreement with the high

⁶⁸ M. J. Jorgenson, *J. Org. Chem.* **27**, 3224 (1962).

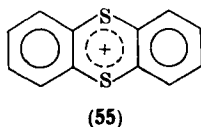
⁶⁹ E. D. Bergmann and M. Rabinowitz, *J. Org. Chem.* **25**, 828 (1960).

⁷⁰ R. Huisgen, E. Laschtuvka, and F. Bayerlin, *Chem. Ber.* **93**, 392 (1960).

^{70a} W. E. Parham, H. Wynberg, W. R. Hasek, P. A. Howell, R. N. Curtis, and W. N. Lipscomb, *J. Am. Chem. Soc.* **76**, 4957 (1954).

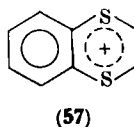
⁷¹ M. M. Kreevoy, *J. Am. Chem. Soc.* **80**, 5543 (1958).

oxidizability of 1,4-dithiin. A similarly successful interpretation has been given of the properties of the dibenzo derivative of **54**, thianthrene.⁷² Solutions of thianthrene in acetic anhydride containing 1% perchloric acid⁷³ or in 96–97% H_2SO_4 ⁷⁴ are paramagnetic; this is probably due to the presence of thianthrene radical cations (**55**) in



these media. This view is supported by a study of ESR, electronic, and near-infrared spectra. ESR spectra of 2,7-dimethyl- and 2,7-dichloro-thianthrene radical cations have also been studied.⁷⁵ The perchlorate and pentachloroantimonate of this cation have been isolated.⁷³

Recently, radical cations of other conjugated sulfur compounds⁷⁶ have been prepared: the radicals derived from 1,4-dithiin (**56**), 1,4-benzodithiin (**57**), and three derivatives of radicals **55** and **57**. Analysis of the ESR spectra of these derivatives permitted the assignment of hyperfine-splitting constants to the six chemically non-equivalent



protons in the radicals **55**–**57**. Lucken⁷⁶ studied the structure of these radicals by the HMO method using both Models A and B and assuming complete planarity. Comparing the results for Model A2 with the experimental hfs constants for radical **56** he arrived at the value 23.2 for the constant Q , which is close to the values obtained for other classes of compounds ($\Delta H_i = Q\rho_i$, where ΔH_i is the hyperfine-splitting constant of the i -th proton, ρ_i is the unpaired-electron density in the i -th position, and Q is a proportionality constant). The agreement between the calculated and experimental hfs constants is significantly better for Model A2 than for Model B ($\delta_s = 1$, $\rho_{CS} = 0.566$).

⁷² A. K. Chandra, *Tetrahedron* **19**, 471 (1963).

⁷³ E. A. C. Lucken, *J. Chem. Soc.* 4963 (1962).

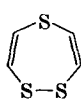
⁷⁴ H. J. Shine and L. Piette, *J. Am. Chem. Soc.* **84**, 4798 (1962).

⁷⁵ H. J. Shine, C. F. Dais, and R. J. Small, *J. Chem. Phys.* **38**, 569 (1963).

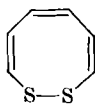
⁷⁶ E. A. C. Lucken, personal communication (1963).

The application of ESR spectral data to the study of conjugated sulfur compounds seems attractive because it could help to resolve the problem of sulfur *d*-orbital participation in conjugation.⁷⁶

d. *Analogues of Cyclodecapentaene (4)*. The prospect of synthesizing these compounds is not particularly encouraging for the reasons stated in the section dealing with analogues of the cyclononatetraenide anion; the HMO treatment¹⁶ makes it seem probable nevertheless that a compound like **58** could be prepared. Compounds **59** and **60**, on the other hand, probably can not.



(58)



(59)



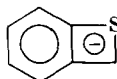
(60)

2. Parent Skeleton: A Non-Alternant Hydrocarbon

a. *Analogues of the Cyclopentadienide Anion (6)*. The five-membered ring system is the smallest odd-membered ring from which a sulfur compound may be derived (at least formally, by Model A). A theoretical treatment¹⁶ of **61** and its benzo derivative **62** indicates that these will be very reactive and quite unstable substances.



(61)



(62)

b. *Analogues of the Tropylium Cation (7)*. Since 1959, when the thiapyrylium ion (**63**) was detected mass spectrometrically⁷⁷ and studied theoretically (Model A),⁷⁸ the thiapyrylium ion⁷⁹ (see also ref. 80) and several of its benzo derivatives (**64–68**)^{80a–84} have been synthesized, largely by Lüttringhaus and his colleagues. Thiaxanthylum cation (**66**), however, was first prepared as early as 1910.⁸¹ The

⁷⁷ V. Hanuš and V. Čermák, *Collection Czech. Chem. Commun.* **24**, 1602 (1959).

⁷⁸ J. Kouřecký, *Collection Czech. Chem. Commun.* **24**, 1608 (1959).

⁷⁹ R. Pettit, *Tetrahedron Letters* No. 23, 11 (1960).

⁸⁰ A. Lüttringhaus and N. Engelhard, *Angew. Chem.* **73**, 218 (1961).

^{80a} A. Lüttringhaus and N. Engelhard, *Chem. Ber.* **93**, 1525 (1960).

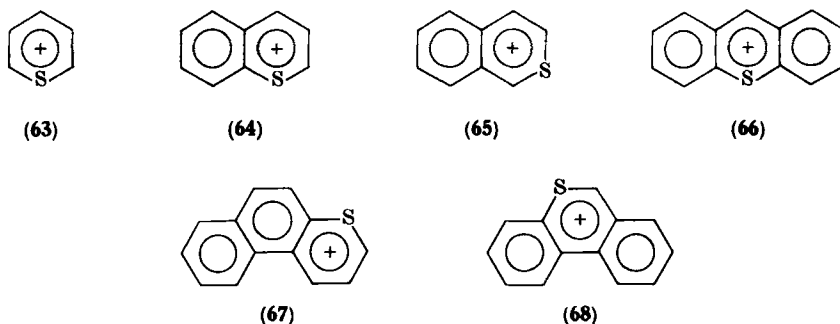
⁸¹ S. Smiles and T. P. Hilditch, *J. Chem. Soc.* **99**, 145 (1910).

⁸² W. Bonthron and D. H. Reid, *Chem. Ind. (London)* 1192 (1960).

⁸³ A. Lüttringhaus, N. Engelhard, and A. Kolb, *Ann. Chem.* **654**, 189 (1962).

⁸⁴ A. Lüttringhaus and A. Kolb, *Z. Naturforsch.* **16b**, 762 (1961).

2,3-benzothiapyrylium ion was synthesized also by Bonthron and Reid.⁸² Models of cations **64**–**66** and **68** have been studied recently by



the HMO and perturbation methods (Models A1 and B),¹⁵ the thiapyrylium cation itself having been previously studied.⁷⁸ According to Model A, cations **63**–**68** are analogues of the tropylium ion and its benzo derivatives. Their properties make it clear that such a comparison is appropriate. Figure 6 presents molecular diagrams of **66** and **67**.

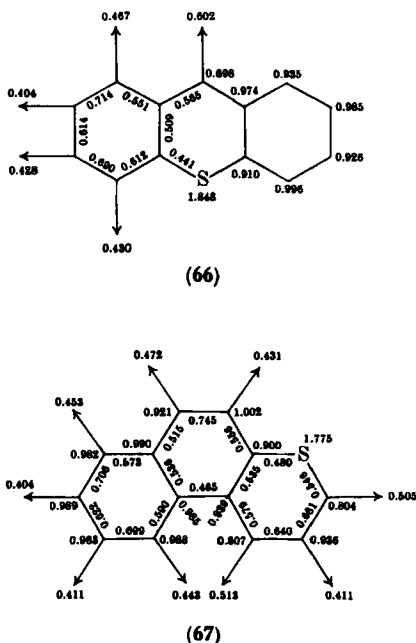


FIG. 6. Molecular diagrams of compounds **66** and **67** (Model A2).¹⁶

These cations undergo electrophilic substitution only reluctantly, being positively charged; on the other hand, they are very reactive towards nucleophilic reagents.

The reaction of 1-benzothiapyrylium ion with phenylmagnesium bromide was studied quantitatively⁸³ and found to yield 2- ($55 \pm 10\%$) and 4-phenylthiochromene ($45 \pm 10\%$). It is worth noting that the relative reactivity is in qualitative agreement with HMO π -electron densities¹⁵ (Model A1, B2), while a perturbation treatment of the benzotropylium cation⁸³ led to the incorrect reactivity order of positions 2 and 4. One must be careful not to overestimate the importance of the agreement or the discrepancy between theory and experiment in this case since the positions belong to different classes. Theory¹⁵ is in agreement with the course of nucleophilic substitution in compound **68**,⁸⁴ which occurs in the position adjacent to the heteroatom.

Like benzo derivatives of thiophene, compounds **63–68** exhibit a correlation between free valence and radical superdelocalizability within the individual classes of positions.¹⁶

Theoretical examination of 2-chlorothiapyrylium and 2-chloro-6-phenylthiapyrylium cations indicates that their stability will be similar to that of the parent ion thiapyrylium.¹⁶

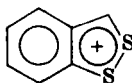
At present, quite a number of derivatives of analogues of the tropylium cation containing two sulfur atoms are known. Both 1,2-⁸⁵ and 1,3-dithiolium cations^{86, 87} (**69** and **70**, respectively) have been synthesized recently; the possible existence of the cation **70** had been



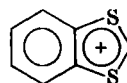
(69)



(70)



(71)



(72)

predicted earlier on the basis of quantum chemical studies.⁸⁸ A successful synthesis of **71** has been reported (cf. ref. 168). Cation **72** is only known in the form of its 5-methyl derivative.⁸⁹ The values of the π -

⁸⁵ E. Klingsberg, *Chem. Ind. (London)* 1568 (1960).

⁸⁶ E. Klingsberg, *J. Am. Chem. Soc.* **84**, 3410 (1962).

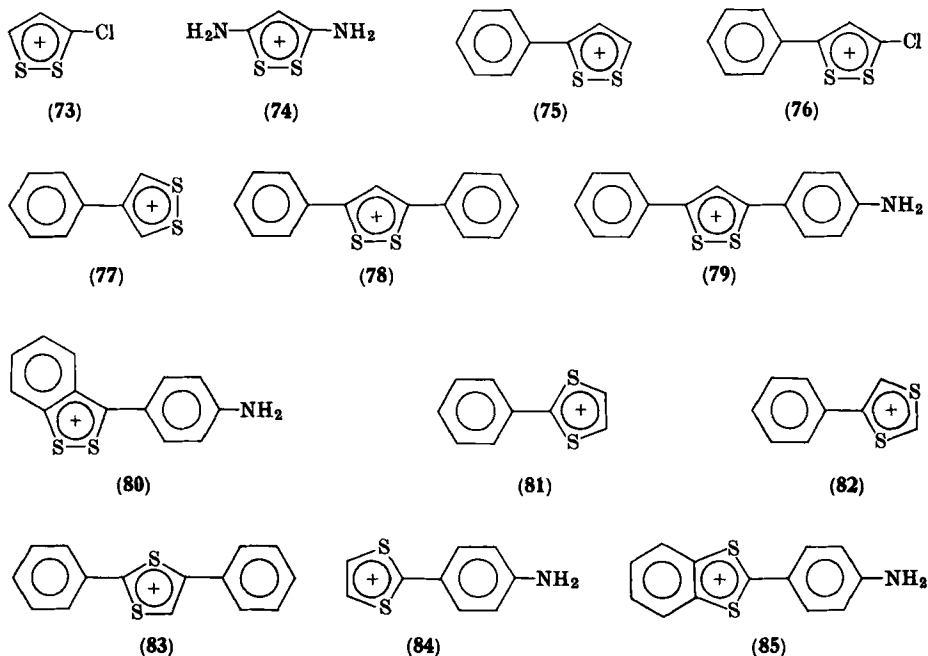
⁸⁷ D. Leaver, W. A. H. Robertson, and D. M. McKinnon, *J. Chem. Soc.* 5104 (1962).

⁸⁸ J. Koutecký, J. Paldus, and R. Zahradník, *Collection Czech. Chem. Commun.* **25**, 617 (1960).

⁸⁹ L. Soder and R. Wizinger, *Helv. Chim. Acta* **42**, 1779, 1733 (1959).

electron densities¹⁵ for **70** and **72** permit a correct prediction of the centers of nucleophilic reactivity.^{86, 89}

Numerous derivatives of **69–72** have been synthesized^{85–87, 89–95} and studied theoretically,¹⁶ e.g. cations **73–85** and some of their



methyl derivatives; references to pertinent experimental work are given in the tables in Section III. So far, data on the reactivity of these ions are scarce; their electronic spectra, however, are quite interesting (see Section III). Unfortunately, in most cases only the positions of the absorption maxima have been reported; these data are often unsatisfactory, at least for theoretical treatments.

Cation **73**, synthesized a short time ago,⁹⁰ is the simplest known derivative of the 1,2-dithiolium ion. Figure 7 presents molecular diagrams of **75** and **77**.

⁹⁰ J. Faust and R. Mayer, *Angew. Chem.* **75**, 573 (1963).

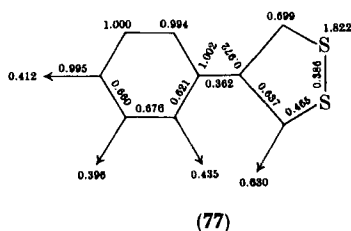
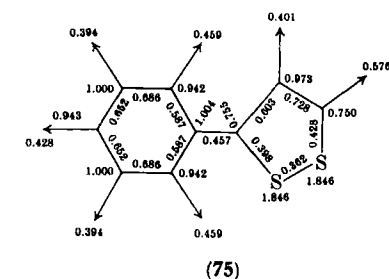
⁹¹ E. Klingsberg, *J. Am. Chem. Soc.* **83**, 2934 (1961).

⁹² E. Klingsberg, *J. Org. Chem.* **28**, 529 (1963).

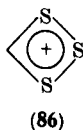
⁹³ E. Klingsberg and A. M. Schreiber, *J. Am. Chem. Soc.* **84**, 2941 (1962).

⁹⁴ D. Leaver and W. A. H. Robertson, *Proc. Chem. Soc. (London)* 252 (1960).

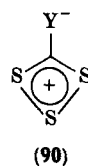
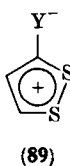
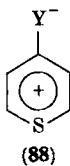
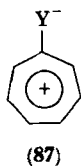
⁹⁵ U. Schmidt, *Chem. Ber.* **92**, 1171 (1959).


 FIG. 7. Molecular diagrams of compounds **75** and **77** (Model A1).¹⁶

There is little hope that cation **86** can be prepared, not just because it contains a four-membered ring, but its energy characteristics are much too unfavorable for it to be a stable compound.

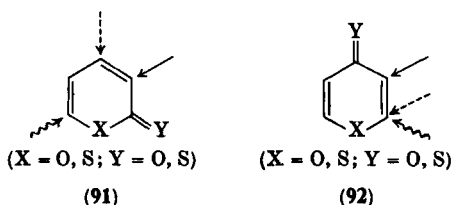


c. *Derivatives of Analogues of the Tropylium Cation: Pyrones and Trithione-like Compounds.* A compound like **87** may be considered as a derivative of the tropylium cation ($Y = O$, tropone; $Y = S$, trophione); molecules **88–90** are analogues of **87**. In formulas **88–90** Y indicates an oxygen or a sulfur atom. Compound **88** represents an



example of 1,4-thiapyrones; **89** is an example of a trithione-like compound. Structure **90** represents an unknown and probably unisolable moiety.

Both 1,2- and 1,4-pyrones (**91** and **92**, respectively) should be mentioned. It also seems appropriate to mention oxygen derivatives of this type, because some properties of these molecules are to a large extent determined by their topology. Properties of the C=Y bonds, the heats of combustion, the UV and IR spectra,⁹⁶ and dipole moment data



(\uparrow , \dagger , and \ddagger , indicate the centers of electrophilic, nucleophilic, and radical substitution, respectively)

suggest that the compounds have a pseudo-aromatic character (for references, see ref. 97). Physical properties as well as various substitution and addition reactions of these compounds have been studied (a review of their chemistry is given in refs. 97 and 97a-c). The course of substitution reactions of 1,4-pyrone and 1,4-thiapyrone^{97a} has been studied in more detail mainly with the intention of judging the "reasonability" of quantum-chemical studies of their electronic structure. The study of polar substitution of 1,2- and 1,4-pyrones is difficult; in electrophilic reactions the substrate is likely to be protonated, thus hindering the reaction, and the situation is further complicated by addition reactions. In nucleophilic reactions, the complicating factor is the decomposition of the primary reaction product. Centers of polar and radical reactivity are indicated in structures **91** and **92**, and it is obvious that the theoretical reactivity of the individual positions is again essentially determined by the

⁹⁶ A. R. Katritzky and R. A. Jones, *Spectrochim. Acta* **17**, 64 (1961).

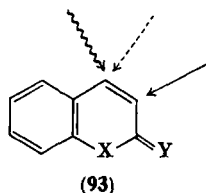
⁹⁷ R. Zahradník, C. Párkányi, and J. Koutecký, *Collection Czech. Chem. Commun.* **27**, 1242 (1962).

^{97a} C. Párkányi and R. Zahradník, *Collection Czech. Chem. Commun.* **27**, 1355 (1962).

^{97b} R. Mayer, *Chem. Ber.* **90**, 2362 (1957).

^{97c} R. Mayer, *Chem. Tech. (Berlin)* **10**, 418 (1958).

topology of the molecules and not by the values of empirical parameters. For the models studied, the order of the reactivity indices for benzo derivatives of 1,2-pyrones¹⁶ is independent of empirical parameters (cf. 93). As an example, the molecular diagram of thiothiacoumarin is shown in Fig. 8.



With the exception of the derivative of 1,4-thiothiapyrone, 3-hydroxy-1,4-pyrones are known compounds.^{98, 99} We are first of all interested in the sulfur heterocycle 3-hydroxy-1,4-thiapyrone which

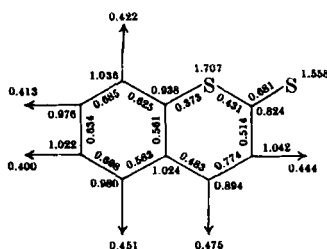


FIG. 8. Molecular diagram of thiothiacoumarin (for parameters see footnote b in Table IX).¹⁶

has only recently been synthesized.^{100, 101} The bond order of the 5-6 bond is relatively high, but since the position of maximum π -electron density does not lie at this bond one is inclined to believe that electrophilic substitution could take place in position 2.¹⁵

Since the synthesis of trithione (89, Y = S) in 1947,¹⁰² scores of papers on related compounds have appeared (see e.g. ref. 103; for

⁹⁸ F. Eiden, *Arch. Pharm.* **292**, 461 (1959).

⁹⁹ F. Eiden, *Arch. Pharm.* **292**, 355 (1959).

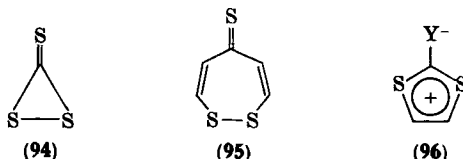
¹⁰⁰ V. Horák and N. Kucharczyk, *Chem. Ind. (London)* 694 (1960).

¹⁰¹ N. Kucharczyk, Thesis, Charles University, Prague, 1960.

¹⁰² B. Böttcher and A. Lüttringhaus, *Ann. Chem.* **557**, 89 (1947).

¹⁰³ F. Challenger, E. A. Mason, E. C. Holdsworth, and R. Emmott, *J. Chem. Soc.* **292** (1953).

additional references, see ref. 15). Compound **94** and the vinylogue of trithione (**95**) are not likely to prove particularly stable. Just as in the unisolable cyclopentadienone, the electronegativity of the exocyclic



atom opposes the tendency of the rings in compounds **94** and **95** to complete a π -electron sextet or decet. The data on the reactivity of trithione¹⁰³ (**89**, $Y = S$) and its isomer **96** ($Y = S$) have been accounted for on the basis of their molecular diagrams.^{15, 104} The facile addition of bromine to isotrithione (**96**)¹⁰³ has been explained¹⁵ by the very high bond order of the 4-5 bond; according to recent findings,¹⁰⁵ however, the addition seems to involve the exocyclic sulfur atom. Recently, the parent skeletons have been rendered available in larger amounts (**89** and **96**, $Y = O, S$)¹⁰⁶ and more detailed data on reactivity may be expected to appear soon; a similar study of the physical and chemical properties of the benzo derivatives of these compounds will be forthcoming.¹⁰⁶

Bergson¹⁰⁷ has studied the electronic structure of trithione (**89**) by a simple SCF (self-consistent field) MO LCAO method (a procedure resembling the ω -technique). The molecular diagram obtained for trithione is presented in Fig. 9 along with its HMO molecular diagram and the HMO molecular diagram of the benzo derivative. The agreement of the calculated¹⁰⁷ and experimental bond lengths¹⁰⁸ in **89** ($Y = S$) is quite satisfactory (the experimental data were obtained with a methyl derivative).

The dimethyl derivative of **95** has an interesting history; this structure was assigned¹⁰⁹ to the product of the reaction of diacetylacetone with P_2S_5 in benzene solution. X-ray analysis^{110, 111} and a quantum-

¹⁰⁴ R. Zahradník and J. Koutecký, *Tetrahedron Letters* No. 18, 632 (1961).

¹⁰⁵ B. Gebhardt and R. Mayer, personal communication (1963).

¹⁰⁶ R. Mayer, personal communication (1963).

¹⁰⁷ G. Bergson, *Arkiv Kemi* **19**, 181 (1962).

¹⁰⁸ W. L. Kehl and G. A. Jeffrey, *Acta Cryst.* **11**, 813 (1958).

¹⁰⁹ F. Arndt, P. Nachtwey, and J. Pusch, *Ber.* **58**, 1638 (1925).

¹¹⁰ S. Bezzi, C. Garbuglio, M. Mammi, and G. Traverso, *Gazz. Chim. Ital.* **88**, 1226 (1958).

¹¹¹ S. Bezzi, M. Mammi, and C. Garbuglio, *Nature* **182**, 247 (1958).

chemical study¹¹² proved that the compound in question has a bicyclic structure of an unusual type (see Section II, E, thiothiophthene).

d. *Analogues of the Cyclononatetraenide Anion (8)*. Low values of the specific delocalization energy, the presence of positions with high

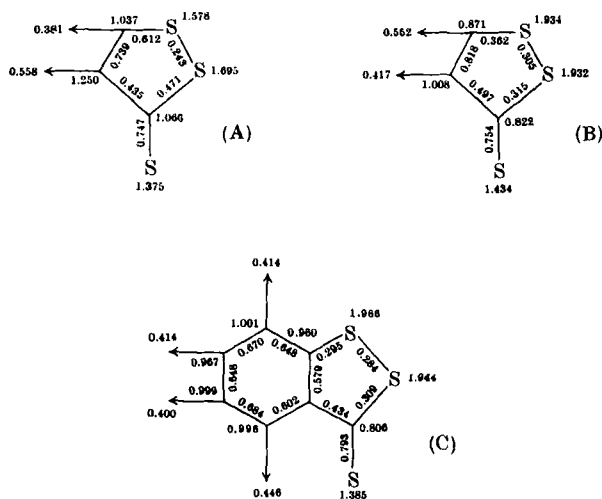
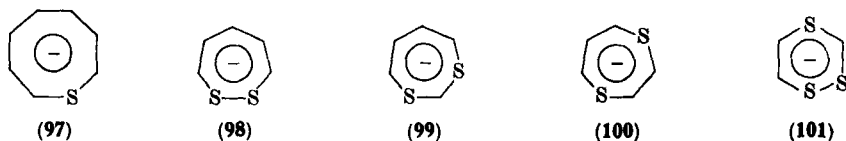


FIG. 9. Molecular diagrams of trithione (A, according to Bergson¹⁰⁷; B, HMO, Model A I, C) and benzotrithione (C).¹⁶

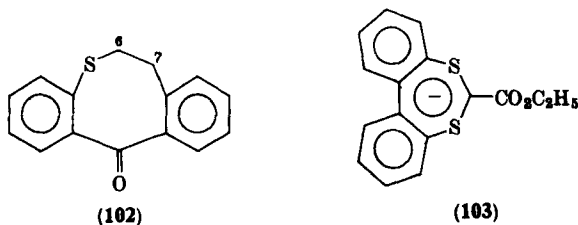
π -electron density, and the high energy of the highest occupied π -molecular orbital (high oxidizability) in the few models of analogues of compound 8 examined theoretically¹⁶ (97–101) indicate that all



these compounds will be quite unstable and difficult to prepare. The most relatively promising synthesis appears to be that of the vinylogue of the 1,2-dithiolium anion (98). Although Model A can be used to estimate the π -electronic energy, it can not be used for the calculation of π -electron densities as it leads to values of $q_s > 2$. Some derivatives

¹¹² G. Giacometti and G. Rigatti, *J. Chem. Phys.* **30**, 1633 (1959).

of the compounds discussed are likely to be prepared in the future; therefore, for example, 7,12-dihydro-6*H*-dibenzo[*b,c*]thiocin-12-one (102),¹¹³ could furnish a dibenzo derivative of 97 by removal of the oxygen atom and dehydrogenation of the 6-7 bond. A short time ago the aromaticity of 103, a derivative of 1,3-dithiepinide anion (99), was discussed in terms of the HMO theory.¹¹⁴ The authors claim that it lacks aromatic properties.



B. ANALOGUES OF BICYCLIC HYDROCARBONS

1. Parent Skeleton: An Alternant Hydrocarbon

An example of compounds belonging to this group are those formally derived from naphthalene by replacing one double bond in each ring by one sulfur atom, e.g. thiophthene (104) whose properties have been studied by perturbation theory in terms of Model A.¹¹⁵ The calculated bond lengths agree well with experimental data¹¹⁶ with the usual exception of the central bond. We believe this is due to the failure to recognize the different character of the central bond. There would probably be no difficulty if a special bond-order-bond-length dependence were used for this type of bond.

The isomeric thienothiophene 105 has been studied theoretically¹⁶; only a dimethyl derivative has been synthesized.¹¹⁷



¹¹³ K. Stach and F. Bickelhaupt, *Angew. Chem.* **74**, 752 (1962).

¹¹⁴ R. Breslow and E. Mohacsi, *J. Am. Chem. Soc.* **85**, 431 (1963).

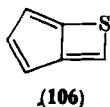
¹¹⁵ M. G. Evans and J. de Heer, *Acta Cryst.* **2**, 363 (1949).

¹¹⁶ E. G. Cox, R. Gillot, and G. A. Jefferey, *Acta Cryst.* **2**, 356 (1949).

¹¹⁷ O. Dann and W. Dimmling, *Chem. Ber.* **87**, 373 (1954).

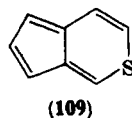
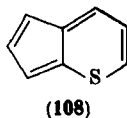
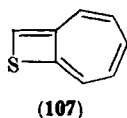
2. Parent Skeleton: A Non-Alternant Hydrocarbon

a. *Analogues of Pentalene (10)*. The parent skeleton has thus far resisted synthetic attempts; pentalene is a typical representative of pseudo-aromatic hydrocarbons as defined by Craig's rule.¹¹⁸ Such hydrocarbons are characterized by the presence of a non-bonding molecular orbital which is either the highest occupied (HOMO) or the lowest free (LFMO) π -molecular orbital in the ground state. Interestingly enough, pentalene has a relatively high value of DE_{sp} . If we pass to the analogue **106**, DE decreases considerably (from 2.45 to 1.77 β);



the non-bonding orbital disappears, however, and the energies of both the HOMO and the LFMO become more favorable. Nevertheless, the system would no doubt still be rather unstable and very easily reduced; additional unfavorable factors probably are the σ -strain in the four-membered ring, and the low π -electron density and high free valence in the position adjacent to the sulfur atom.

b. *Analogues of Azulene (11)*. Three sulfur analogues (**107–109**) can be derived from azulene by use of the Longuet-Higgins model.



Whereas **107** is at present unknown, the rather unstable compounds **108** and **109** (the earlier predicted^{118a} thialene¹¹⁹ and isothialene,^{120, 121} respectively) have been synthesized and their properties studied both experimentally and theoretically. Figure 10 presents the HMO orbital energies of azulene and of compounds **107–109**. Much work on the chemistry of the derivatives of these compounds has been done by

¹¹⁸ D. P. Craig, *J. Chem. Soc.* 3175 (1951).

^{118a} R. Mayer, *Angew. Chem.* **69**, 481 (1957).

¹¹⁹ R. Mayer, J. Franke, V. Horák, I. Hanker, and R. Zahradník, *Tetrahedron Letters* No. 9, 289 (1961).

¹²⁰ A. G. Anderson, Jr. and W. F. Harrison, *Tetrahedron Letters* No. 2, 11 (1960).

¹²¹ A. G. Anderson, Jr., W. F. Harrison, R. G. Anderson, and A. G. Osborne, *J. Am. Chem. Soc.* **81**, 1255 (1959).

Mayer and his colleagues^{106, 122, 123} and by Leaver *et al.*¹²⁴ Two benzo derivatives of thialene have been prepared, **110** and **111** (Fig. 11); various 1,3-disubstituted products of electrophilic substitution reactions^{120, 121} (in agreement with theory) of isothialene and its various

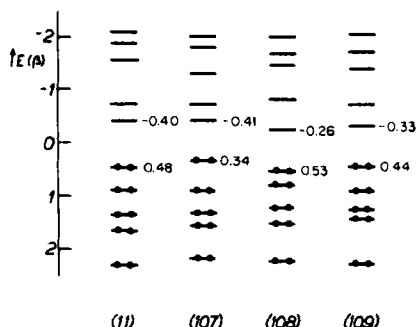
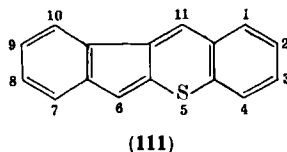
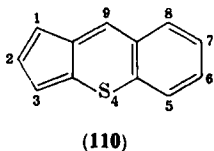
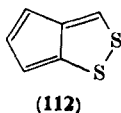


FIG. 10. HMO orbital energies of azulene (**11**) and its sulfur analogues **107–109** (Model A1).^{15,16}

methyl and dimethyl derivatives have also been synthesized.¹⁰⁶ Further, phenyl derivatives¹²⁴ and aza analogues of **110** and **111** were prepared and their electronic spectra discussed: The 2-phenyl derivative of **110**, the 11-aza analogue of **111**, and a triphenyl derivative of benzo[*g*]thialene.¹²⁵



According to theoretical calculations,¹⁶ synthesis of an azulene analogue formally derived by replacing two C=C double bonds in the seven-membered ring by two sulfur atoms seems feasible (cf. **112**).



¹²² R. Mayer and H. Russ, *Chem. Ber.* **95**, 1311 (1962).

¹²³ R. Mayer and U. Weise, *Naturwissenschaften* **45**, 312 (1958).

¹²⁴ D. Leaver, J. Smolicz, and W. H. Stafford, *J. Chem. Soc.* 740 (1962).

¹²⁵ G. V. Boyd, *J. Chem. Soc.* 55 (1959).

c. *Analogues of Heptalene (12)*. The successful synthesis of this typical pseudo-aromatic hydrocarbon was reported only a few years ago.¹²⁶ An HMO treatment yields a non-bonding HOMO. A similar

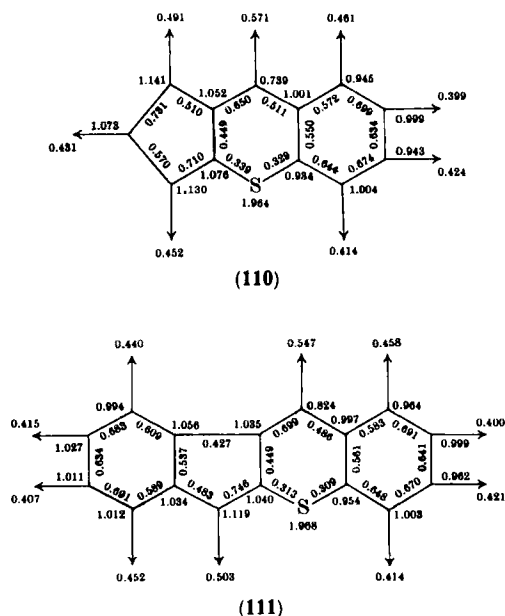
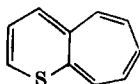
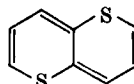


FIG. 11. Molecular diagrams of compounds **110** and **111** (Model A1).¹⁶

treatment of **113** and particularly **114** (Model A) leads to weakly bonding HOMO's. Despite the decrease in the values of DE , the delocalization energy of the model of **114** remains rather high (2.26β);



(113)

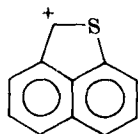


(114)

this circumstance as well as the relatively favorable values of reactivity indices make it probable that these two substances could be prepared.

¹²⁶ H. J. Dauben, Jr. and D. J. Bertelli, *J. Am. Chem. Soc.* **83**, 4658 (1961).

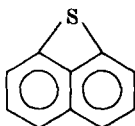
non-bonding orbital (Model A¹⁶); it will probably be less stable than the parent perinaphthyl system (13).



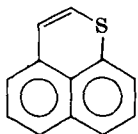
(116)

2. Parent Skeleton: A Non-Alternant Hydrocarbon

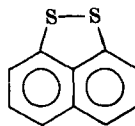
Of the compounds 117–119, only the last two have been studied experimentally (see, e.g., refs. 129–131); all have been investigated theoretically. A prediction of reactivity based on π -electron densities and superdelocalizabilities¹⁶ is not unambiguous. Some properties of 119 and its relatively low dipole moment are discussed in ref. 129.



(117)



(118)



(119)

D. ANALOGUES OF DIPHENYL- AND FULVALENE-LIKE HYDROCARBONS

1. Parent Skeleton: An Alternant Hydrocarbon

Although various interesting analogues of diphenyl (16) and terphenyl (see, e.g., ref. 132) have been prepared, no theoretical studies devoted to these compounds have appeared so far.

2. Parent Skeleton: A Non-Alternant Hydrocarbon

Compounds belonging to this group have not as yet been prepared. Prospects for the synthesis of the sulfur analogue of fulvalene (17) are not especially promising; the HMO energy characteristics and the

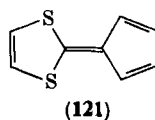
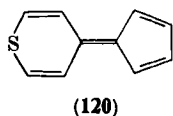
¹²⁹ H. Lumbroso and Ch. Marschalk, *J. Chim. Phys.* **48**, 123 (1951).

¹³⁰ W. B. Price and S. Smiles, *J. Chem. Soc.* 2372 (1928).

¹³¹ N. N. Vorozheev and V. Ya. Rodionov, *Dokl. Akad. Nauk SSSR* **134**, 1085 (1960).

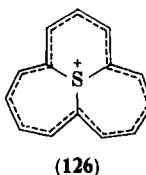
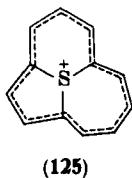
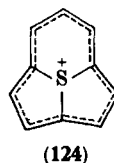
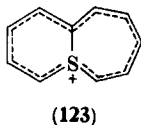
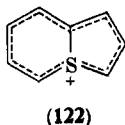
¹³² H. Wynberg and A. Bantjes, *J. Am. Chem. Soc.* **82**, 1447 (1960).

molecular diagrams¹⁶ of the analogues **120** and **121** of sesquifulvalene (**18**) are more encouraging, however.



E. ANALOGUES OF HYDROCARBONS DERIVED BY SUBSTITUTING SULFUR FOR A TERTIARY CARBON ATOM

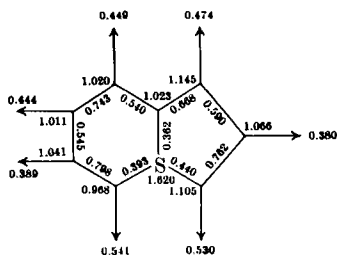
These compounds, at present hypothetical, contain a σ -tervalent sulfur atom. Theoretical studies were performed¹⁶ for models of compounds **122**–**126**; the first two are, in a sense, analogues of bicyclic compounds. In view of their formal similarity with the cyclazines,¹³³ and their positive charge, the tricyclic compounds **124**–**126** shall be called "cyclotholia."



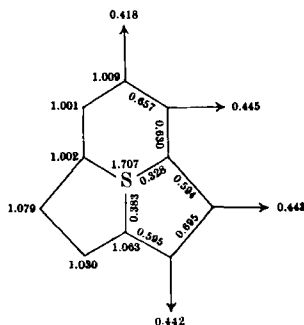
Supposing that the sulfur d -orbitals do not participate in conjugation one can imagine that three hybrid $3sp^2$ orbitals are occupied by one electron each (forming the C—S σ -bonds by overlap with $2sp^2$ orbitals of carbon atoms) and the $3p_z$ orbital by two electrons. The sulfur atom evidently bears a charge of +1 due to the presence of only one electron in the orbital that originally was a non-bonding atomic orbital; consequently, the charge is localized. Models of **122**–**126** have been studied using Model B2. The values of the HOMO energies make it clear that **123** would have two electrons in an anti-bonding and **125** two in a

¹³³ R. J. Windgassen, Jr., W. H. Saunders, and V. Boekelheide, *J. Am. Chem. Soc.* **81**, 1459 (1959).

non-bonding π -molecular orbital. In this regard, the remaining compounds appear more promising, although **126** would be readily oxidizable. Compounds **122** and **124** seem capable of existence; their molecular diagrams are presented in Fig. 13.



(122)



(124)

FIG. 13. Molecular diagrams of compounds **122** and **124** (Model B 2).¹⁶

Another compound that can be mentioned is 2,5-dimethylthiophene,^{110-112, 134} to which can be ascribed structure **127** on the basis of a study of its crystal and molecular structure.¹³⁴ Oxygen and selenium analogues have a similar structure¹³⁴ (however, see ref. 134a). Both quantum-chemical treatments reported^{112, 135-137} lead to similar

¹³⁴ M. Mammi, R. Bardi, C. Garbuglio, and S. Bezzi, personal communication (1961).

^{134a} H. G. Hertz, G. Traverso, and W. Walter, *Ann. Chem.* **625**, 43 (1959).

¹³⁵ K. Maeda, *Bull. Chem. Soc. Japan* **33**, 1466 (1960).

¹³⁶ K. Maeda, *Bull. Chem. Soc. Japan* **34**, 785 (1961).

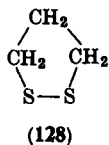
¹³⁷ K. Maeda, *Bull. Chem. Soc. Japan* **34**, 1166 (1961).

conclusions. In the first case sulfur was assumed to participate in conjugation by p_z orbitals only (in addition, interaction between the sulfur p_x orbitals was taken into account)¹¹²; in the second pd -hybridization of sulfur orbitals was considered.¹³⁵⁻¹³⁷



F. OTHER HETEROCYCLIC COMPOUNDS

Considerable attention has been paid to the calculation of steric strain in dithiolane (**128**), which value is of importance for checking the hypothesis of Calvin et al.¹³⁸ concerning the biological importance of



6-thioctic acid. Reference 139 summarizes the present state of knowledge and provides data for 1,2-dithiolane-4-carboxylic acid. An MO treatment¹⁴⁰ of the S—S bond in **128** has explained the difference in the spectra of cyclic and aliphatic disulfides. Special attention was paid to $3p\pi$ interaction of the sulfur orbitals (cf. ref. 141).

Compound **129** was investigated in a general study of cyclic systems of alternating atoms A and B.¹⁴² The salient result was that the requirements for aromaticity in compounds in which the conjugated system is formed of $p\pi$ - and $d\pi$ -orbitals differ substantially from those for the more usual cyclic systems composed of atoms with only $p\pi$ -orbitals, e.g. sometimes the necessary condition for aromaticity is the presence of an octet rather than a sextet of conjugated electrons. Craig¹⁴³ has

¹³⁸ J. A. Barltrop, P. M. Hayes, and M. Calvin, *J. Am. Chem. Soc.* **76**, 4348 (1954).

¹³⁹ G. Bergson and L. Schotte, *Acta Chem. Scand.* **12**, 367 (1958).

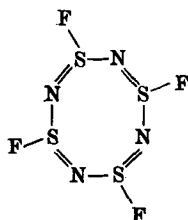
¹⁴⁰ G. Bergson, *Arkiv Kemi* **12**, 233 (1958).

¹⁴¹ L. Pauling, *Proc. Nat. Acad. Sci. U.S.* **35**, 495 (1949).

¹⁴² D. P. Craig, *J. Chem. Soc.* 997 (1959).

¹⁴³ D. P. Craig, *Chem. Soc. (London), Spec. Publ. No. 12*, p. 343 (1958).

studied in particular sulfur compounds of this type with regard to the properties of *d*-orbitals.



(129)

G. BRIEF SURVEY OF THEORETICAL STUDIES OF OTHER SULFUR-CONTAINING COMPOUNDS

Since there are relatively few quantum chemical studies of sulfur compounds it seems appropriate to refer briefly to papers dealing with sulfur compounds of types that lie outside the scope of the present review. Excitation energies of $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions have been calculated and compared with experimental data, and molecular diagrams have been published for a series of thiocarbamic acid derivatives¹⁴⁴⁻¹⁴⁶ and for thioamides and thiohydrazides¹⁴⁷ (see also ref. 147a). Energy characteristics and molecular diagrams have been calculated for thio derivatives of uracil and purine,¹⁴⁸ arylisothiocyanates,¹⁴⁹ and various bis-thiocarbonyl compounds.⁶¹ Excitation energies of thioacetamide have been calculated by the CI(configuration interaction) MO LCAO method.¹⁵⁰ The electronic structures of sulfoxides and sulfones have also been investigated.¹⁵¹⁻¹⁵³

¹⁴⁴ M. J. Janssen, Thesis, Chemical Institut T.N.O., Utrecht, 1959.

¹⁴⁵ M. J. Janssen, *Rec. Trav. Chim.* **79**, 464 (1960).

¹⁴⁶ M. J. Janssen, *Rec. Trav. Chim.* **79**, 1066 (1960).

¹⁴⁷ J. Sandström, *Acta Chem. Scand.* **16**, 1616 (1962).

^{147a} J. Sandström, *Acta Chem. Scand.* **17**, 678 (1963).

¹⁴⁸ B. Pullman and A. Pullman, "Results on Quantum Mechanical Calculations of the Electronic Structure of Biochemicals." University of Paris, Paris, 1960.

¹⁴⁹ R. Zahradník, D. Vlachová, and J. Koutecký, *Collection Czech. Chem. Commun.* **27**, 2336 (1962).

¹⁵⁰ H. Hosoya, J. Tanaka, and S. Nagakura, *Bull. Chem. Soc. Japan* **33**, 850 (1960).

¹⁵¹ T. Jordan, H. W. Smith, L. L. Lohr, Jr., and W. N. Lipscomb, *J. Am. Chem. Soc.* **85**, 846 (1963).

¹⁵² H. P. Koch and W. Moffitt, *Trans. Faraday Soc.* **47**, 7 (1951).

¹⁵³ W. Moffitt, *Proc. Roy. Soc. (London)* **200A**, 409 (1950).

H. THERMOCHEMISTRY, GEOMETRICAL STRUCTURE, AND INFRARED SPECTRA

Studies belonging in this section are mentioned only very briefly since none of them includes a quantum-chemical treatment; they are of indirect importance for such a treatment, however.

Resonance energies have been reported¹⁵⁴ (see also ref. 154a) for a few conjugated sulfur compounds: thiolacetic acid (4–5 kcal mole⁻¹), thiourea (27 kcal mole⁻¹), thiosemicarbazide (28 kcal mole⁻¹), thiophene (20 kcal mole⁻¹), and thianthrene (17 kcal mole⁻¹ difference between the resonance energy of thianthrene and that of two benzene molecules). These values were calculated from the heats of combustion and bond energies, which are 61.5 kcal for the C—S, 115 kcal for the C=S, 87.5 kcal for the S—H, and 67 kcal for the S—S bonds.¹⁵⁵ Calorimetry of sulfones has been studied intensively.¹⁵⁶

Abrahams¹⁵⁷ has thoroughly treated data on the geometrical configuration of sulfur compounds in general, due attention being paid to heterocyclic systems. The article compiles numerous data on bond angles and bond lengths in sulfur compounds; experimental data are interpreted chiefly in terms of hybridization of sulfur atomic orbitals. A graph is included which shows the dependence of the C—S bond length on the percent double bond character.

An exhaustive review of infrared spectral studies of sulfur compounds appeared in 1963.¹⁵⁸

III. Electronic and Charge-Transfer Spectra

It has been recently demonstrated that quantities derived from the simple MO theory can also be used successfully to correlate excitation energies of the first maxima in the electronic spectra of various sulfur compounds. At the same time, this method is incapable of solving such a basic problem as the assignment of absorption bands to electronic

¹⁵⁴ S. Sunner, *Acta Chem. Scand.* **9**, 847 (1955).

^{154a} S. Sunner, *Acta Chem. Scand.* **17**, 728 (1963).

¹⁵⁵ S. Sunner, *Acta Chem. Scand.* **9**, 837 (1955).

¹⁵⁶ W. K. Busfield, K. J. Ivin, H. Mackle, and P. A. G. O'Hare, *Trans. Faraday Soc.* **57**, 1064 (1961).

¹⁵⁷ S. C. Abrahams, *Quart. Rev. (London)* **10**, 407 (1956).

¹⁵⁸ A. R. Katritzky and A. P. Ambler, in "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), p. 161, Vol. II. Academic Press, New York, 1963.

transitions; satisfactory results were obtained only upon application of the method of limited configuration interaction. This method, however, has only been applied to a few sulfur compounds: thiophene,⁴¹ dithiin,⁴¹ and thioacetamide.¹⁵⁰

Excitation energies calculated for thiophene and dithiin (and furan)⁴¹ by the method of Pariser and Parr are in good agreement with the experimental energies. In the case of thiophene (as well as furan), interaction between all mono-excited configurations and selected bi-excited configurations was considered; in the case of 1,4-dithiin, interaction between mono-excited configurations, with the exception of those involving a transition of an electron from the lowest level, was considered. Hückel's MO's were used for the calculations. Interestingly

TABLE IV
MOLECULAR WAVE FUNCTIONS OF 1,4-DITHIIN AND THEIR
ENERGIES⁴¹

Energy (eV)	Wave function
-269.78	$\psi_0 = 0.998 \chi_0 + 0.0630 \chi_{3 \rightarrow 6}$
-265.17	$\psi_1 = 0.9904 \chi_{4 \rightarrow 5} + 0.1381 \chi_{2 \rightarrow 6}$
-263.97	$\psi_2 = \chi_{4 \rightarrow 6}$
-263.89	$\psi_3 = \chi_{3 \rightarrow 5}$
-263.50	$\psi_4 = 0.0630 \chi_0 - 0.9980 \chi_{3 \rightarrow 6}$

enough, the first absorption band of furan corresponds to an almost pure $3 \rightarrow 4$ transition (energy levels are numbered consecutively from 1 to 5 starting with that of lowest energy), whereas the first band of thiophene belongs chiefly to the configuration $\chi_{2 \rightarrow 4}$ (with an admixture of configurations $\chi_{1 \rightarrow 4}$ and $\chi_{3 \rightarrow 5}$) and the configuration $\chi_{3 \rightarrow 4}$ represents the main contribution to the next higher molecular wave function only. These results are encouraging rather than definitive, and the compounds obviously need to be studied systematically. In the case of 1,4-dithiin, the molecular wave functions have a particularly simple form owing to molecular symmetry, and individual bands can be assigned to almost "pure" transitions between molecular orbitals. The wave functions and corresponding energies are given in Table IV.

Aside from attempts to interpret the electronic spectrum of thio-phenene in terms of the MO method,^{13, 31, 33, 34, 39, 41} successful use of the

TABLE V
ELECTRONIC SPECTRA OF THIOPHENE-LIKE HETEROCYCLES AND RELATED COMPOUNDS^{16,17}

Compound	Solvent ^a	$\lambda(\text{m}\mu)$	$\tilde{\nu}(\text{kcm}^{-1})$	$\log \epsilon$	$E(N \rightarrow V_1)^b$	Reference (absorption spectrum)
Thiophene	I	236 243 ^c	42.4 41.2	3.8 3.6	1.717	17
Benzene ^d	M-E	207	48.3	3.9	2.000	161
Benzo[<i>b</i>]thiophene	E	290	34.5	3.3	1.388	17
Benzo[<i>c</i>]thiophene	M	343	29.2	3.8	0.996	106
Naphthalene ^d	E	285	35.1	3.6	1.236	161
Dibenzothiophene	E	286	35.0	4.1	1.349	17
Naphtho[2,1- <i>b</i>]thiophene	C	304	32.9	4.1	—	162
Naphtho[1,2- <i>b</i>]thiophene	C	304	32.9	3.5	—	162
Phenanthrene ^d	E	293	34.1	4.2	1.210	161
Naphtho[2,3- <i>b</i>]thiophene	C	352	28.4	3.8	—	162
Anthracene ^d	M-E	375	26.7	3.9	0.828	161
Phenanthro[9,10- <i>c</i>]thiophene	CH	338	29.6	3.7	1.177	163
Triphenylene ^d	M-E	284	35.2	4.3	1.367	161
Benzo[<i>b</i>]naphtho[2,1- <i>d</i>]thiophene	I	349	28.6	3.6	1.140	164
Chrysene ^d	E	319	31.3	4.2	1.040	161
Benzo[<i>b</i>]naphtho[2,3- <i>d</i>]thiophene	MC	369	27.1	3.5	0.994	165
Benz[<i>a</i>]anthracene ^d	E	359	27.9	3.8	0.905	161
Diphenyl sulfide	E	274	36.5	3.7	1.432	17
Stilbene ^d	I	308 322 ^c	32.5 31.1	4.4 4.1	1.009	161

^a C, cyclohexane; CH, chloroform; E, 95% ethanol; I, isooctane; M, methanol; and MC, methycyclohexane.

^b Heterocycles: parameters B3; hydrocarbons; the usual HMO approximation.

^c Shoulder. ^d Parent hydrocarbon.

VB method has been reported.^{29a} The VB method has also been used to study the spectrum of diphenylsulfide.¹⁵⁹

Janssen¹⁴⁴⁻¹⁴⁶ has successfully used a method resembling the ω -technique (self-consistence within the HMO framework) to study the spectral properties of derivatives of thiocarbamic acid and thiourea; these compounds lie outside the scope of this review, however. The possibility of using the HMO method to correlate excitation energies of the first (usually intense) bands of various classes of heterocyclic compounds has been investigated; see, e.g., refs. 15, 17, and 160. The

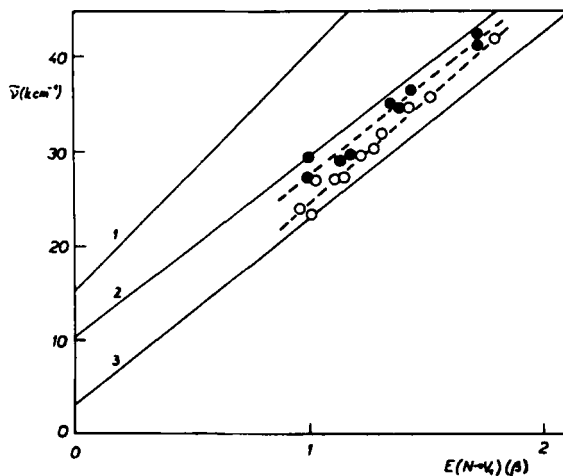


FIG. 14. Correlation of experimental and theoretical excitation energies of the maxima of the first bands of benzothiophenes (●) and 1,2- and 1,4-pyrones (○). Polyenes (1), benzenoid hydrocarbons (2), and benzotropyia (3).

compounds in question were hetero analogues of alternant (e.g., thiophene) and non-alternant hydrocarbons (e.g., thiopyrylium ion and thialene), and analogues of tropone and trophothione. The study of the first class of compounds proved simplest owing to the similarity of the absorption curves of the heterocycles (thiophenes) to those of

¹⁵⁹ A. Mangini and C. Zauli, *J. Chem. Soc.* 4960 (1956).

¹⁶⁰ J. Koutecký, J. Paldus, and R. Zahradník, *J. Chem. Phys.* **36**, 3129 (1962).

¹⁶¹ E. Clar, "Aromatische Kohlenwasserstoffe." Springer, Berlin, 1952.

¹⁶² W. Carruthers and J. R. Crowder, *J. Chem. Soc.* 1932 (1957).

¹⁶³ O. Dann, M. Kokurudz, and R. Gropper, *Chem. Ber.* **87**, 140 (1954).

¹⁶⁴ O. Kruber and G. Grigoleit, *Chem. Ber.* **87**, 1895 (1954).

¹⁶⁵ E. G. G. Werner, *Rec. Trav. Chim.* **68**, 520 (1949).

parent hydrocarbons. The results of experimental and theoretical studies are summarized in Table V. Figure 14 shows a fairly close correlation between the experimental and theoretical data, the regression line lying in the vicinity of that for benzenoid hydrocarbons. The same figure also shows the regression lines for additional classes of hydrocarbons. It has been demonstrated¹⁶⁰ that the splitting in the plot of $\tilde{\nu}_{exp}$ against $E(N \rightarrow V_1)$ into several partial dependences is due to the varying contributions of the electronic repulsion integrals to the total excitation energies for various classes of substances; put in another way, these integrals have a character of structure-dependent quantities. Table VI presents the constants of the regression line of the

TABLE VI
CONSTANTS IN THE EQUATION $\tilde{\nu}(\text{kcm}^{-1}) = aE(N \rightarrow V_1) + b^{23, 160}$

Compounds	<i>a</i>	<i>b</i>	<i>r^a</i>	<i>n^b</i>
Benzothiophenes	19.865	7.478	0.974	8
1,2- and 1,4-Pyrones	22.179	2.415	0.990	10
Benzenoid hydrocarbons	19.207	10.234	0.982	44
Benzotropyliia	19.90	2.83	0.996	7

^a Correlation coefficient.

^b Number of compounds.

above-mentioned dependence along with the constants corresponding to the data for benzenoid hydrocarbons and benzotropyliia.

Equally interesting is the situation in the second class of compounds studied (analogues of non-alternant hydrocarbons), which is best divided into two sub-groups; analogues of the tropylium ion and analogues of azulene. The empirical correlation of experimental and theoretical excitation energies studied requires a further subdivision into compounds with one heteroatom (e.g. thiopyrylium ion) and two heteroatoms, either adjacent (e.g., 1,2-dithiolium ion) or non-adjacent (e.g., 1,3-dithiolium ion). Experimental and theoretical data are presented in Table VII. Table VIII summarizes data for the derivatives of dithiolia. Figure 15 shows the absorption curves of 1-benzo-

¹⁶⁶ E. Heilbronner and J. N. Murrell, *Mol. Phys.* **6**, 1 (1963).

¹⁶⁷ A. Lüttringhaus and N. Engelhard, *Chem. Ber.* **93**, 1525 (1960).

¹⁶⁸ A. Lüttringhaus, M. Mohr, and N. Engelhard, *Ann. Chem.* **661**, 84 (1963).

TABLE VII
ELECTRONIC SPECTRA OF THIOPYRYLIA, DITHIOLIA, THIALENE, AND RELATED COMPOUNDS^{15,16}

Compound	Solvent ^a	$\lambda(\text{m}\mu)$	$\tilde{\nu}(\text{kc}\text{m}^{-1})$	$\log \epsilon$	$E(N \rightarrow V_1)^b$	$E(N \rightarrow V_1)^c$	Reference (absorption spectrum)
Thiopyrylium ^d	H ₂ O (1% HClO ₄)	284	35.2	3.6	1.289	1.477	80
1,2-Dithiolium ^d	E (HClO ₄)	288	34.7	3.6	1.143	1.255	87
1,3-Dithiolium ^d	E (HClO ₄)	254	39.4	3.6	1.064	1.345	87
Tropylium ^e	conc. H ₂ SO ₄	274	36.5	3.7	1.692	—	166
1-Benzothiopyrylium ^d	A (1% HClO ₄)	384	26.0	3.5	0.953	0.992	167
2-Benzothiopyrylium ^d	A (1% HClO ₄)	384	26.0	3.5	0.884	0.972	167
1,2-Benzodithiolium ^d	A (1% HClO ₄)	381	26.2	3.6	0.879	—	168
5-Methyl-1,3-benzodithiolium ^d	H ₂ O (20% HClO ₄)	319	31.4	3.8	0.960	0.972	16
		352 ^{sh}	28.4	3.6	—	—	—
Thienotropylium ^d	H ₂ O	408	24.5	3.3	1.117	—	169
Benzotropylium ^e	60% H ₂ SO ₄	425	23.5	3.3	1.028	—	166
Dibenzo[<i>b,d</i>]thiopyrylium ^d	A (1% HClO ₄)	460	21.7	2.9	—	—	84
Dibenzo[<i>a,c</i>]tropylium ^e	conc. H ₂ SO ₄	457	21.9	4.1	0.928	—	166
Naphtho[2,1- <i>b</i>]thiopyrylium	—	—	—	—	—	0.908	—
Naphthotropylium ^e	60% H ₂ SO ₄	458	21.8	3.5	0.980	—	166
Thialene	C	528 ^f	18.9	—	0.837	0.823	119
Isothialene	H	542 ^f	18.5	2.5	0.869	0.839	121
Azulene	C	582 ^f	17.2	2.5	0.877	—	166
Benzo[<i>b</i>]thialene	D	522 ± 5 ^g	19.2	~ 2.2	0.746	—	106
Benz[<i>f</i>]azulene	C	557 ^f	18.0	2.5	0.739	—	166
Dibenzo[<i>b,f</i>]thialene	D	505 ± 5 ^g	19.8	3.2	0.734	—	106
Dibenz[<i>a,g</i>]azulene	—	—	—	—	0.715	—	—

^a A, acetic acid; C, cyclohexane; D, dioxane; E, ethanol; and H, hexane.

^c Model A 2.

^d Perchlorate.

^e Sulfate.

^f Band center.

^b Model A 1 or the usual HMO approximation.

^g The long-wavelength band has no fine structure.

TABLE VIII
ELECTRONIC SPECTRA OF PHENYL AND DIMETHYLAMINOPHENYL DERIVATIVES OF DITHIOLIA
AND RELATED COMPOUNDS

Compound	Solvent ^a	$\lambda(\text{m}\mu)$	$\tilde{\nu}(\text{kcm}^{-1})$	$\log \epsilon$	$E(N \rightarrow V_1)^b$	Reference (absorption spectrum)
3-Methyl-5-phenyl-1,2-dithiolium ^c	E (HClO ₄)	354	28.2	4.3	0.937	87
4-Phenyl-1,2-dithiolium ^d	0.1N HCl	345	29.0	3.1	0.909	85
3,5-Diphenyl-1,2-dithiolium ^c	E (HClO ₄)	381	26.2	4.4	0.883	87
2-Phenyl-4-methyl-1,3-dithiolium ^c	E (HClO ₄)	362	27.6	4.2	0.864	87
2-Methyl-4-phenyl-1,3-dithiolium ^c	E (HClO ₄)	310	32.2	3.9	0.825	87
4-Phenyl-1,3-dithiolium	E (HClO ₄)	306	32.7	3.9	0.825	87
2,4-Diphenyl-1,3-dithiolium ^c	E (HClO ₄)	392	25.5	4.2	0.725	87
3-(4'-Dimethylaminophenyl)-5-phenyl-1,2-dithiolium	—	557	17.9	—	0.653	93
2-(4'-Dimethylaminophenyl)-1,3-dithiolium ^e	—	515	19.4	—	0.720	86
3-(4'-Dimethylaminophenyl)-1,2-benzodithiolium ^c	0.1N HCl (E)	588	17.0	4.5	0.695	93
5-Methyl-2-(4'-dimethylaminophenyl)-1,3-benzodithiolium ^c	A	536	18.7	—	0.708	89

^a A, acetic acid; E, ethanol.

^b Models: A 1, C.

^c Perchlorate.

^d Sulfate.

^e Iodide.

thiopyrylium and 5-methyl-1,3-benzodithiolium ions and also that of the parent benzotropylium ion for the sake of comparison. Even though the character of the absorption curve in the near-UV region is apparently the same for all of these compounds, there is a striking bathochromic shift of the first maximum when going from 5-methyl-1,3-benzodithiolium to benzotropylium cation, whereas the $E(N \rightarrow V_1)$ energies of models of these compounds are rather similar. This shows quite clearly that these compounds must be considered as members of different structural groups of substances. The limited experimental data (and the lack of uniform experimental conditions) and insufficient theoretical knowledge of the spectra of these compounds prevent for the present a correlation of the experimental and theoretical excitation

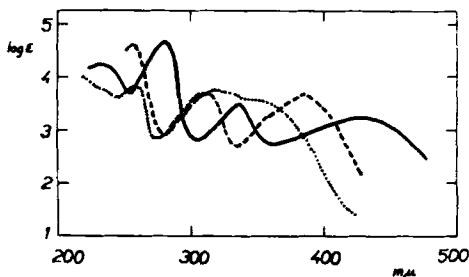
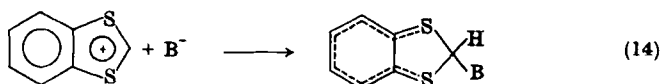


FIG. 15. Absorption spectra of benzotropylium (—), 1-benzothiopyrylium (---), and 5-methyl-1,3-benzodithiolium cations (.....). For references and experimental conditions, see Table VII.

energies by the HMO method, although it is quite clear that it will be possible to evaluate the data for these compounds by means of this method.

The sensitivity of the shape of the absorption curve of 5-methyl-1,3-benzodithiolium to changes in the medium is illustrated in Fig. 16. The situation with analogous compounds is likely to be similar. As soon as a sufficiently strong nucleophile is present in the solution, the reaction shown in Eq. (14) seems to occur.



Using data presented in Tables VII and VIII it may be shown that the data for thiopyrylia and 1,2- and 1,3-dithiolia in the plot of $\bar{\nu}_{\text{exp}}$

against $E(N \rightarrow V_1)$ lie on separate straight lines whose slopes are higher than that of the line for benzotropylium and increase in the order of the classes mentioned. It is worth mentioning that the point corresponding to the only known analogue of benzotropylium with an intact

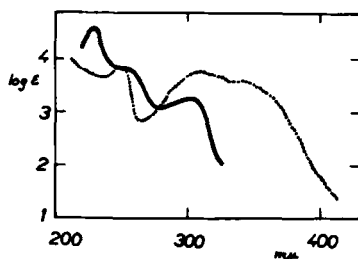
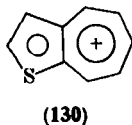


FIG. 16. Absorption spectra of the 5-methyl-1,3-benzodithiolium cation in 20% aqueous perchloric acid (. . .) and in 1% perchloric acid in 95% ethanol (—).¹⁶

seven-membered ring, 2,3-thienotropylium cation (**130**), prepared in a remarkable way a short time ago,¹⁶⁹ lies exactly on the regression line for benzotropylium.



In the case of thialenes and related compounds it proved necessary to work with the center of the visible absorption band (corresponding to the $1 \rightarrow 1'$ transition) for the treatment to be homogeneous, since this band is structureless in some of these compounds. Like the data for parent systems, the data for sulfur analogues of azulenes lie in the region $0.7\text{--}0.9\beta$ and $17\text{--}20 \text{ kcm}^{-1}$. The data are concentrated in this region in agreement with the finding that the contribution of the electronic repulsion integral to the excitation energy is very small in comparison to that in other classes of compounds.¹⁷⁰ Absorption curves of the sulfur analogues and the parent azulenes are quite similar (Fig. 17).

A satisfactory correlation is found between the energy of the first

¹⁶⁹ D. Sullivan and R. Pettit, *Tetrahedron Letters* No. 6, 401 (1963).

¹⁷⁰ J. Kouřecký, personal communication, 1963.

intense maximum in the electronic spectra and the $E(N \rightarrow V_1)$ values of the pyrones (Table IX). Figure 14 shows that the data lie in the region between the regression lines for benzenoid hydrocarbons and for benzotropyia. Table X presents spectral data for some additional sulfur heterocycles belonging to various classes. Quite interesting is the case of the sulfur-aza analogue of benzoheptalene,¹²⁷ whose absorption maximum in 0.1*N* HCl is shifted bathochromically by 58 m μ against that of the unprotonated form, while the theoretical $E(N \rightarrow V_1)$ value for the model of the N-protonated substance is higher by more than

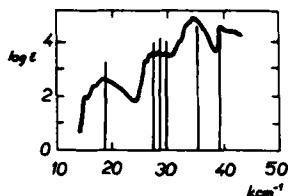


FIG. 17. Absorption spectrum of benz[*f*]azulene¹⁶⁶; positions of maxima in the spectrum of benzo[*b*]thialene¹⁰⁶ are indicated.

0.2 β . It may be concluded that in 0.1*N* HCl the compound suffers some change other than the assumed N-protonation, provided there is no misinterpretation.

The origin of $\pi \rightarrow \pi$ charge-transfer bands may be explained in terms of the HMO theory by excitation of an electron from the highest occupied π -molecular orbital of the donor to the lowest free π -molecular orbital of the acceptor (e.g., see refs. 174–176). Conjugated hydrocarbons, their analogues, and certain derivatives are among the most important π -donors, while tetracyanoethylene, chloranil, and 1,3,5-trinitrobenzene are typical examples of π -acceptors. For complexes of hydrocarbons with various acceptors, linear relations have been found to exist between the excitation energy of the maximum of the first charge-transfer band and the HOMO energy of the donor (for a series of complexes with a constant acceptor); the same relationship holds for complexes of various derivatives. Of the sulfur compounds, only complexes of aliphatic sulfur compounds had been studied until

¹⁷⁴ M. Chowdhury and S. Basu, *Trans. Faraday Soc.* **56**, 335 (1960).

¹⁷⁵ M. J. S. Dewar and A. R. Lepley, *J. Am. Chem. Soc.* **83**, 4560 (1961).

¹⁷⁶ M. Nepraš and R. Zahradník, *Tetrahedron Letters* No. 2, 57 (1963).

TABLE IX

ELECTRONIC SPECTRA OF THIAPYRONES, DITHIONES, TRITHIONES, AND RELATED COMPOUNDS^{15,16,97}

Compound	Solvent ^a	$\lambda(\text{m}\mu)$	$\tilde{\nu}(\text{cm}^{-1})$	$\log \epsilon$	$E(N \rightarrow V_1)$	Reference (absorption spectrum)
1,2-Pyrone	E	289	34.6	3.7	1.426 ^b	97
5,6-Dimethyl-1,2-pyrone	C	305	32.8	3.7	1.426 ^b	97
2-Thio-1,2-thiapyrone	C	431	23.2	3.6	1.013 ^b	97
1,4-Pyrone	C	238	42.0	4.0	1.789 ^b	97
1,4-Thiapyrone	C	280	35.7	4.2	1.520 ^b	97
4-Thio-1,4-pyrone	C	330	30.3	4.2	1.279 ^b	97
4-Thio-1,4-thiapyrone	C	371	27.0	4.3	1.114 ^b	97
Coumarin	H	312	32.0	3.7	1.309 ^b	171
Thiacoumarin	H	338	29.6	3.4	1.223 ^b	171
Thiocoumarin	H	373	26.8	4.1	1.031 ^b	171
Thiothiacoumarin	H	416	24.0	4.0	0.968 ^b	171
3-Hydroxy-1,4-pyrone	M	272	36.8	4.0	1.291 ^b	99
3-Hydroxy-1,4-thiapyrone	E	360	27.8	3.5	1.119 ^b	101, 172
3-Hydroxy-4-thio-1,4-pyrone	M	353	28.3	4.3	1.089 ^b	98
1,2-Dithia-4-cyclopenten-3-one	C	310	32.2	3.6	1.257 ^c	106
1,2-Dithia-4-cyclopentene-3-thione	C	415	24.1	3.8	1.013 ^c	106
1,3-Dithia-4-cyclopenten-2-one	C	257	38.9	3.5	1.288 ^c	106
1,3-Dithia-4-cyclopentene-2-thione	C	363	27.5	4.2	1.123 ^c	103, 106
Benzo-1,2-dithia-4-cyclopenten-3-one	C	350	28.6	3.5	1.171	106
Benzo-1,2-dithia-4-cyclopentene-3-thione	C	429	23.3	3.9	1.068 ^c	106
Benzo-1,3-dithia-4-cyclopentene-2-thione	C	367	27.2	> 4	1.124	106

^a C, cyclohexane; E, ethanol; H, *n*-hexane; M, methanol.^c Model A 1, C.

^b Parameters: $\delta_{\text{O}(\text{endo})} = \delta_{\text{O}(\text{exo})} = 2$ $\rho_{\text{CS}(\text{endo})} = 0.7$
 (Model B) $\delta_{\text{S}(\text{endo})} = 1$ $\rho_{\text{CS}(\text{exo})} = 0.9$
 $\delta_{\text{S}(\text{exo})} = 0.5$ $\rho_{\text{CO}(\text{endo})} = 1.1$
 $\rho_{\text{CO}(\text{exo})} = \sqrt{2}.$

TABLE X
ELECTRONIC SPECTRA OF MISCELLANEOUS SULFUR COMPOUNDS¹⁶

Compound	Solvent ^a	$\lambda(m\mu)$	$\tilde{\nu}(kcm^{-1})$	$\log \epsilon$	$E(N \rightarrow V_1)$	Reference (absorption spectrum)
Dibenzo[<i>b,f</i>]thiepin	E	295	33.9	3.7	0.718 ^b	69
Thianthrene	P	~ 300 sh	33.3	~ 2.9	—	173
Benzo[<i>b</i>]tropolthiazine	M	412	24.3	3.8	0.630 ^c	127
	M, 0.1N HCl	470	21.3	3.8	0.865 ^c	127
Thiaphenylene	E	420	23.8	3.2	1.229 ^c	181
1,8-Naphthylene disulfide	—	363	27.6	—	—	131

^a E, ethanol; P, petroleum ether; M, methanol.

^b Model B 3.

^c Model A 1, C.

¹⁷¹ A. Mangini and D. Dal Monte, *Atti Accad. Sci. Ist. Bologna* 5, 20 (1958).

¹⁷² V. Horák, personal communication, 1963.

¹⁷³ L. Láng, "Absorption Spectra in the Ultraviolet and Visible Region," Part II. Akadémiai Kiadó, Budapest, 1961.

recently when complexes of a group of sulfur heterocycles with tetracyanoethylene and chloranil were investigated.¹⁷⁷ Table XI includes data for some compounds of other types as well. It is apparent from the excitation energies that the complexes are mostly colored. The view that the absorption bands observed are due to charge-transfer complexes and not to decomposition products is supported by the finding that the energies given in Table XI under headings A and B are

TABLE XI
ENERGIES OF THE MAXIMA OF THE FIRST CHARGE-TRANSFER BANDS OF
COMPLEXES OF SULFUR COMPOUNDS WITH TETRACYANOETHYLENE (A)
AND CHLORANIL (B) IN CHLOROFORM¹⁷⁷

Compound	$\tilde{\nu}(\text{kcm}^{-1})$		HOMO (β)	
	A	B	A1	B3
Thiophene	24.7 22.3 sh	24.8	0.769	0.691
Benzo[b]thiophene	20.9 18.6	22.3 21.0 sh	0.668	0.566
Dibenzothiophene	17.8	20.5	0.665	0.576
Dinaphthothiophene	12.6	14.7	$\sim 0.48^a$	$\sim 0.40^a$
Methyl phenyl sulfide	17.4	19.2	—	—
Diphenyl sulfide	16.9	19.4	0.677	0.465
Diphenyl disulfide	19.0	22.1	—	—
Thianthrene	21.7 16.5	23.9 19 sh	—	—
Di- <i>n</i> -butyl sulfide	19.0	21.5	—	—

^a Estimated.

mutually linearly dependent. Although plotting the experimental excitation energies against the energy of the HOMO of the acceptor (see Table XI) does not lead to a particularly close linear correlation, it is obvious that for parameters B3 the data lie approximately in the region of regression lines corresponding to the correlation of excitation energies of benzenoid hydrocarbons with the same acceptors.¹⁷⁶

¹⁷⁷ M. Nepraš and R. Zahradník, *Collection Czech. Chem. Commun.* **29**, 1555 (1964).

IV. Aromaticity of Sulfur Compounds

Several widely differing interpretations of the concept of aromaticity (see ref. 4 and references therein) are encountered in the literature. In the present review higher delocalization energy and stability and a lower reactivity as well as a tendency to undergo substitution rather than addition reactions are taken to indicate high aromaticity. Since experimental delocalization energies are available for only a very small number of sulfur compounds (see Section II, H) and because detailed experimental information on reactivity is likewise available for only a limited number of sulfur compounds, an attempt has to be made to utilize the theoretical values of the delocalization energy and the quantities that provide information about the reactivity of the molecule as a whole (HOMO and LFMO energies) as well as about the reactivity of individual positions (A , S , q) and bonds (p , A_o).¹⁷⁸

It may be said that the condition necessary for a molecule to be aromatic is a relatively high specific delocalization energy (DE divided by either the number of bonds over which the conjugated system extends or the number of electrons in conjugation) and that the sufficient condition is a relatively low reactivity (judged by the values of theoretical indices) under the conditions under which aromaticity is to be exhibited. Such a "theoretical aromaticity" (Ar) can be expressed formally as :

$$Ar = f(DE_{sp}, \text{HOMO}, \text{LFMO}, X_{ext}),$$

where X_{ext} is the chemical reactivity index of the most reactive position or bond. Since the form of the functional dependence is not known, aromaticity must be estimated quite empirically by comparing the theoretical characteristics of a model of the compound investigated with the characteristics of a compound of known aromaticity. It should be added that the specific delocalization energy is a quantity depending on the extent of the conjugated system and on the structural type to which the compound belongs. Figure 18 presents the plots of DE/m (m is the number of bonds involved in conjugation) against the number of electrons in conjugation, n , for several classes of hydrocarbons (the individual points are not given). The same figure shows the data for benzothiophenes and benzothiopyrylia for both Models

¹⁷⁸ Discussions with Dr. J. Koutecký and Dr. J. Michl of this Institute contributed to elucidation of these problems.

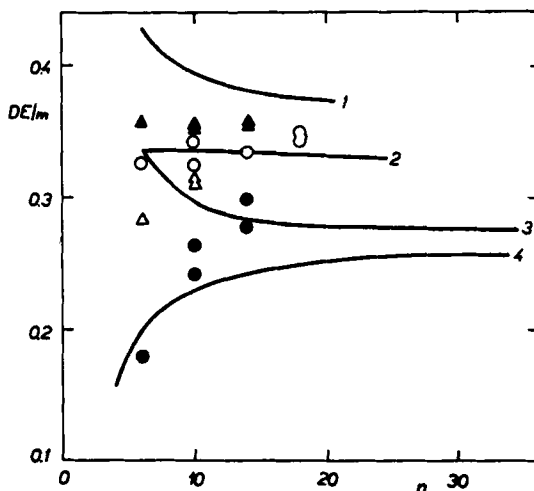


FIG. 18. Benzotropylium (1), polyacenes (2), cyclopolyenes (3) and polyenes (4). Thiophenes: \circ , \bullet ; benzothiopyrylia; Δ , \blacktriangle . Model A: solid points, Model B: outlined marks. For explanation see text.

A and B. DE values were calculated from the W values given in Section IV, A for the Kekulé structures of types 131 and 132. The data for benzothiophenes (Fig. 18) make it clear that Model A1 yields DE



values which are too low and Model B3 values which are too high. This is irrelevant for comparisons inside a group of structurally related compounds. According to Model A it is evident (and obviously correct) that all sulfur heterocyclic compounds have a lower DE value than do the corresponding parent hydrocarbons.

To illustrate the presently adopted meaning of the term "aromaticity," let us cite an example: 1- and 2-benzothiopyrylia are unstable (non-aromatic) in media containing OH^- ions in spite of their relatively high DE/m value owing to the presence in the molecules of positions with low π -electron densities. On the other hand, under the usual conditions of electrophilic substitution these compounds appear

unusually stable (highly aromatic). This is true because not only do their molecules have a high specific delocalization energy but they also have neither a position with high π -electron density nor a bond with a high bond order.

V. Concluding Remarks

Even though quantum-chemical studies of sulfur compounds have not yet developed to such an extent as those of oxygen and especially nitrogen compounds, it is clear that it is possible also in this area to both successfully interpret experimental data and contribute to a more rational investigation of organic compounds. One of the causes of the slower progress in the application of theory to this field has probably been the uncertainty connected with the selection of a suitable model for sulfur atom orbitals in conjugation. It has become evident, however, that this problem is not so fundamental within the HMO framework for two reasons: First, it has been found in numerous cases that both models of σ -bivalent sulfur (that considering and that not considering the d -orbital participation in conjugation) lead to the same conclusions; this holds for both quantities derived from molecular orbital energies and for those derived from molecular orbital expansion coefficients. Second, in the cases where it is not clear how to use Model A, satisfactory results may be obtained by using Model B. More specifically, Model A (unmodified) fails to predict correctly the reactivity of various benzo derivatives of thiophenes and leads to unrealistic values of the π -electron densities with analogues of cyclic anions. Moreover it is rather difficult to apply in the case of more sophisticated quantum-chemical methods, such as the CI MO LCAO method, as well as in the HMO treatment of compounds of σ -tervalent sulfur.

As for the prediction of the reactivity of sulfur heterocyclic compounds, the q , F , and p values rather than atom localization energies or exact superdelocalizabilities yield correct information. This can be tentatively explained by the conclusion reached by Brown⁵⁰ in his study on the reactivity of pyridine-like heterocycles: he has shown that the course of readily occurring reactions is determined by the ground state π -electron distribution, while orientation in reluctantly occurring reactions, in which there is considerable electron reorganization in the transition state, is essentially in agreement with atom-localization energies. The reactions that have been studied so far (electrophilic

substitution of thiophenes and nucleophilic substitution of thiopyrylia and dithiolia) obviously belong to the former type (in this connection, see refs. 57 and 58). A systematic and serious study in this field will no doubt be forthcoming.

As far as the electronic spectra of sulfur compounds are concerned, previous experience^{4, 15, 17, 97, 144-146, 160, 179-182} concerning correlations of experimental excitation energies of the first bands with the theoretical values of excitation energies can be reaffirmed. This means that the HMO method is successfully applicable even in this field provided that spectra of as extensive sets of structurally closely related compounds as possible are treated. The spectra must be recorded under comparable experimental conditions; this requirement is especially severe with various organic ions.

In view of the remarkably swift development of the chemistry of sulfur heterocycles, an extension of quantum-chemical calculations to various additional physical properties as well as a more systematic approach in both experimental and theoretical studies can be expected in the near future. Even though it is not possible to put forward responsibly an optimum unique set of HMO empirical parameters, Model B ($\delta_s = 1$, $\delta_{C(s)} = 0.1$, $\rho_{CS} = 0.7$) may perhaps be recommended for the beginning of a systematic treatment. As for other parameters, the set given by Streitwieser⁴ can be recommended; the value 0.5 has proved suitable for ρ_{SS} . It is quite obvious, however, that such studies should develop simultaneously with application of more sophisticated methods, above all the configuration interaction method.⁴²

VI. Appendix

A. ENERGY CHARACTERISTICS

Table XII summarizes HMO quantities referring to models of sulfur compounds: total π -electronic energy (W), energies of the two highest occupied molecular orbitals (k_2 and k_1 ; k_1 is referred to as HOMO in the text), energies of the two lowest free molecular orbitals (k_{-1} and k_{-2} ; k_{-1} is referred to as LFMO in the text), and the energy

¹⁷⁹ C. A. Coulson and R. Daudel, "Dictionary of Values of Molecular Constants." Mathematical Inst., Oxford, and Centre de Chimie Théorique de France, Paris, 1955.

¹⁸⁰ G. Naville, H. Strauss, and E. Heilbronner, *Helv. Chim. Acta* **43**, 1243 (1960).

¹⁸¹ S. O'Brien and D. C. C. Smith, *J. Chem. Soc.* 2907 (1963).

¹⁸² E. Heilbronner and J. N. Murrell, *J. Chem. Soc.* 2611 (1962).

TABLE XII
ENERGY CHARACTERISTICS^a (β -UNITS)

Compound (structural formula)	<i>n</i>	Para- meters	<i>W</i>	<i>k</i> ₂	<i>k</i> ₁	<i>k</i> ₋₁	<i>k</i> ₋₂	<i>E</i> (<i>N</i> → <i>V</i> ₁)	Ref- erence
Thiirene (25)	4	A 1	4.0000	1.6000	0.4000	-0.4000	-1.6000	0.8000	16
		B 2	3.9998	1.8485	0.1514	-1.0000	—	1.1514	16
Cyclobutadiene (1)	4	—	4.0000	2.0000	0.0000	0.0000	-2.0000	—	—
Thiophene (26)	6	A 1	7.0754	—	0.7689	-0.7689	—	1.5378	17
		B 3	7.6337	—	0.6913	-1.0256	—	1.7169	17
Benzene (2)	6	—	8.0000	1.0000	1.0000	-1.0000	-1.0000	2.0000	179
Benzo[<i>b</i>]thiophene (Thianaphthene) (27)	10	A 1	12.9029	—	0.6677	-0.6677	—	1.3354	17
		B 3	13.4188	—	0.5660	-0.8223	—	1.3883	17
Benzo[<i>c</i>]thiophene (Isothianaph- thene) (28)	10	A 1	12.6574	—	0.4381	-0.4381	—	0.8762	17
		B 3	13.2374	—	0.3534	-0.6429	—	0.9963	17
Naphthalene (9)	10	—	13.6832	1.0000	0.6180	-0.6180	-1.0000	1.2360	179
Dibenzothiophene (29)	14	A 1	18.7794	—	0.6645	-0.6645	—	1.3290	17
		B 3	19.2563	—	0.5761	-0.7726	—	1.3487	17.
Naphtho[1,2- <i>c</i>]thiophene (33)	14	A 1	18.4611	0.7483	0.4857	-0.4857	-0.7483	0.9714	16
Phenanthrene	14	—	19.4492	0.7691	0.6052	-0.6052	-0.7691	1.2104	179
Benzo[<i>b</i>]naphtho[2,3- <i>d</i>]thiophene(34)	18	B 3	24.9215	0.6993	0.4325	-0.5616	-0.8841	0.9941	16
Benz[<i>a</i>]anthracene	18	—	25.1012	0.7150	0.4523	-0.4523	-0.7150	0.9046	179
Benzo[<i>b</i>]naphtho[2,1- <i>d</i>]thiophene(35)	18	B 3	24.9785	0.7144	0.4790	-0.6614	-0.8216	1.1404	16
Chrysene	18	—	25.1900	0.7923	0.5201	-0.5201	-0.7923	1.0402	179
Phenanthro[9,10- <i>c</i>]thiophene (36)	18	B 3	24.8801	0.6739	0.4805	-0.6963	-0.8253	1.1768	16
Triphenylene	18	—	25.2745	0.6840	0.6840	-0.6840	-0.6840	1.3680	179
1,2,3-Thiadiazole	6	A 1,C	8.1230	—	—	—	—	1.4592	56
1,2,4-Thiadiazole	6	A 1,C	8.1920	—	—	—	—	1.5414	56
1,2,5-Thiadiazole	6	A 1,C	8.1585	—	—	—	—	1.4427	56
1,3,4-Thiadiazole	6	A 1,C	8.1542	—	—	—	—	1.5771	56
2,1,3-Benzothiadiazole	10	A 1,C	14.4427	1.0000	0.6104	-0.4543	-1.1907	1.0647	16
Tetracyanothiophene (40)	14	A 1,C	22.0202	0.9170	0.6795	-0.3290	-0.5948	1.0085	16

TABLE XII—continued

Compound (structural formula)	<i>n</i>	Para- meters	<i>W</i>	<i>k</i> ₂	<i>k</i> ₁	<i>k</i> ₋₁	<i>k</i> ₋₂	<i>E</i> (<i>N</i> → <i>V</i> ₁)	Ref- erence
1,2-Dithiete (37)	6	A 1	6.6093	0.9023	0.8336	-0.8336	-0.9023	1.6672	16
1,2-Benzodithiete (46)	10	A 1,C	12.5125	0.8883	0.7334	-0.7334	-0.8883	1.4668	16
Dithia-1,2-diazete (45)	6	A 1,C	7.6402	1.0448	0.9427	-0.5000	-0.8774	1.4427	16
Dicyano-1,2-dithiete (39)	10	A 1,C	14.1008	0.8890	0.7492	-0.4293	-0.8461	1.1785	16
Thiepin (51)	8	A 1	9.2186	1.2315	0.2143	-0.2143	-1.2315	0.4286	16
Cyclooctatetraene (3)	8	—	9.6568	1.4142	0.0000	0.0000	-1.4142	1.4142	—
Dibenzo[<i>b,f</i>]thiepin (52)	16	B 3	21.5825	0.7406	0.2294	-0.4888	-0.9760	0.7182	16
1,2-Dithiin (53)	8	A 1,C	8.9036	1.1421	0.3338	-0.3338	-1.1421	0.6676	16
1,4-Dithiin (54)	8	A 1	8.6648	1.1662	0.4000	-0.4000	-1.1662	0.8000	16
		B 2	8.6228	1.0000	0.1514	-1.0000	-1.3115	1.1514	16
Tetracyano-1,4-dithiin (41)	16	A 1,C	23.6867	0.9203	0.4198	-0.1848	-0.5213	0.6046	16
Thietide ^b (61)	6	A 1	5.5388	0.7922	0.2810	-1.2810	-1.4884	1.5620	16
Cyclopentadienide ^b (6)	6	—	6.4722	0.6180	0.6180	-1.6180	-1.6180	2.2360	—
Thiapyrylium ^c (63)	6	A 1	8.0876	1.1327	1.0898	-0.1986	-0.6275	1.2887	15
		A 2	8.5037	1.1949	1.1591	-0.3181	-0.5293	1.4772	15
		B 2	8.257	—	1.000	-0.348	—	1.348	—
Tropylium ^c (7)	6	—	8.9879	1.2470	1.2470	-0.4450	-0.4450	1.6920	180
1-Benzothiapyrylium ^c (64)	10	A 1	13.898	—	0.842	-0.111	—	0.953	15
		A 2	14.2645	1.034	0.8178	-0.1737	-0.6063	0.9915	15
		B 2	14.037	—	0.808	-0.228	—	1.036	15
2-Benzothiapyrylium ^c (65)	10	A 1	13.801	—	0.741	-0.143	—	0.884	15
		A 2	14.2151	1.1299	0.7680	-0.2037	-0.5315	0.9717	15
		B 2	13.957	—	0.678	-0.294	—	0.971	15
Benzotropylium ^c	10	—	14.7040	1.1557	0.8019	-0.2261	-0.5550	1.0280	180
Thiaxanthylum ^c (66)	14	A 2	20.0339	1.0000	0.7044	-0.1112	-0.5856	0.8156	16
Dibenzo[<i>a,d</i>]tropylium ^c	14	—	20.4217	1.0000	0.6639	-0.1598	-0.5043	0.8237	180
Naphtho[2,1- <i>b</i>]thiapyrylium ^c (67)	14	A 2	20.0297	0.9065	0.7033	-0.2047	-0.5042	0.9080	16
Naphtho[2,1]tropylium ^c	14	—	20.4740	0.9145	0.7031	-0.2773	-0.4450	0.9804	180
2-Chlorothiapyrylium ^c	8	A 1,C	12.1609	1.1312	1.0464	-0.2189	-0.6326	1.6653	16

2-Chloro-6-phenylthiapyrylium ^c	14	A 1,C	20.6191	1.0000	0.7879	-0.1793	-0.5983	0.9672	16
1,2-Dithiolium ^c (69)	6	A 1	7.570	—	1.015	-0.128	—	1.143	15
		B 2	7.752	—	0.900	-0.400	—	1.300	15
1,3-Dithiolium ^c (70)	6	A 1	7.160	—	0.932	-0.131	—	1.064	15
		A 2	8.0092	1.1591	1.0706	-0.2744	-0.5293	1.3450	—
		B 2	7.569	—	0.763	-0.418	—	1.181	—
1,2-Benzodithiolium ^c (71)	10	A 1,C	13.3742	1.0580	0.8006	-0.0782	-0.6801	0.8788	16
1,3-Benzodithiolium ^c (72)	10	A 1	13.0494	0.9546	0.8625	-0.0978	—	0.9603	88
		A 2	13.8116	1.0465	0.8296	-0.1423	-0.6304	0.9720	88
3,5-Diamino-1,2-dithiolium ^c (74)	10	A 1,C	12.9783	0.8168	0.6146	-0.5926	-0.7011	1.2072	16
3-Phenyl-1,2-dithiolium ^c (75)	12	A 1,C	16.0526	1.0000	0.8365	-0.1003	-0.6736	0.9368	16
4-Phenyl-1,2-dithiolium ^c (77)	12	A 1,C	15.9451	1.0000	0.7813	-0.1279	-0.5823	0.9092	16
3,5-Diphenyl-1,2-dithiolium ^c (78)	18	A 1,C	24.5237	0.8553	0.7998	-0.0828	-0.6489	0.8826	16
3-(4'-Aminophenyl)-5-phenyl-1,2-dithiolium ^c (79)	20	A 1,C	27.0292	0.8380	0.5229	-0.1315	-0.6589	0.6544	16
3-(4'-Aminophenyl)-1,2-benzodithiolium ^c (80)	18	A 1,C	24.4188	0.8181	0.5662	-0.1287	-0.6799	0.6949	16
2-Phenyl-1,3-dithiolium ^c (81)	12	A 1	15.7053	1.0000	0.7700	-0.0942	-0.6275	0.8642	16
4-Phenyl-1,3-dithiolium ^c (82)	12	A 1	15.5853	1.0000	0.6984	-0.1263	-0.5224	0.8247	16
2,4-Diphenyl-1,3-dithiolium ^c (83)	18	A 1	24.1303	1.0000	0.6333	-0.0915	-0.5208	0.7248	16
2-(4'-Aminophenyl)-1,3-dithiolium ^c (84)	14	A 1,C	18.2382	0.9532	0.5493	-0.1709	-0.6275	0.7202	16
2-(4'-Aminophenyl)-1,3-benzodithiolium ^c (85)	18	A 1,C	24.1553	0.8623	0.5794	-0.1283	-0.7138	0.7077	16
— (86)	6	A 1,C	7.0026	1.0624	0.9448	-0.0949	-0.6817	1.0397	16
2-Thio-1,2-pyrone	8	B ^d	—	—	0.423	-0.729	—	1.153	97
1,2-Thiapyrone	8	B ^d	—	—	0.720	-0.573	—	1.292	97
1,2-Pyrone	8	B ^d	—	—	0.733	-0.692	—	1.426	97
2-Thio-1,2-thiapyrone	8	B ^d	—	—	0.443	-0.570	—	1.013	97
1,4-Pyrone	8	B ^d	—	—	0.979	-0.810	—	1.789	97
1,4-Thiapyrone	8	B ^d	—	—	0.873	-0.647	—	1.520	97
4-Thio-1,4-pyrone	8	B ^d	—	—	0.493	-0.786	—	1.279	97
4-Thio-1,4-thiapyrone	8	B ^d	—	—	0.478	-0.636	—	1.114	97
Coumarin	12	B ^d	21.4868	0.8446	0.8044	-0.5046	-1.0744	1.3090	16

TABLE XII—continued

Compound (structural formula)	<i>n</i>	Para- meters	<i>W</i>	<i>k</i> ₂	<i>k</i> ₁	<i>k</i> ₋₁	<i>k</i> ₋₂	<i>E</i> (<i>N</i> → <i>V</i> ₁)	Ref- erence
Thiacoumarin	12	B ^a	19.0987	0.8144	0.7706	-0.4526	-1.0536	1.2232	16
Thiocoumarin	12	B ^a	18.3214	0.8442	0.5254	-0.5054	-1.0657	1.0308	16
Thiothiacoumarin	12	B ^a	15.9528	0.7976	0.5106	-0.4571	-1.0503	0.9677	16
3-Hydroxy-1,4-pyrone	10	B ^a ,C	—	—	0.4802	-0.8104	—	1.2906	97
3-Hydroxy-1,4-thiapyrone	10	B ^a ,C	—	—	0.4710	-0.6475	—	1.1180	97
		A 1,C	17.5741	0.9942	0.5945	-0.4358	-0.7761	1.0303	97
3-Hydroxy-4-thio-1,4-pyrone	10	B ^a ,C	—	—	0.3021	-0.7865	—	1.0886	97
1,2-Dithiacyclopenten(4)-one(3)	8	A 1,C	12.527	—	0.849	-0.408	—	1.257	15
1,2-Dithiacyclopentene(4)-thione(3)	8	A 1,C	9.4249	1.0639	0.5914	-0.4213	-0.7012	1.0127	15
1,3-Dithiacyclopenten(4)-one(2)	8	A 1,C	12.257	—	0.755	-0.534	—	1.288	15
1,3-Dithiacyclopentene(4)-thione(2)	8	A 1,C	9.154	—	0.592	-0.532	—	1.123	15
Benzo-1,2-dithiacyclopentene(4)- thione(3)	12	A 1,C	15.3191	0.8920	0.6313	-0.4370	-0.6805	1.0683	16
1,2-Dithiepinide ^b (98)	10	A 1,C	10.1412	0.5905	0.0938	-0.8957	-0.9167	0.9895	16
1,3-Dithiepinide ^b (99)	10	A 1	9.6770	0.4668	0.1188	-0.6921	-1.0000	0.8109	16
1,4-Dithiepinide ^b (100)	10	A 1	9.7915	0.5765	0.0864	-0.8114	-0.9621	0.8978	16
1,2,4-Trithiinide ^{b,c} (101)	10	A 1,C	9.2307	0.5816	0.0646	-0.7695	-0.9332	0.8341	16
Cyclononatetraenide ^b	10	—	15.5176	0.3473	0.3473	-1.0000	-1.0000	1.3473	—
Thieno[2,3- <i>c</i>]thiophene (105)	10	A 1	11.9323	0.9137	0.5260	-0.5260	-0.9137	1.0520	16
— (106)	8	A 1	9.7695	0.9163	0.5184	-0.0801	-1.2250	0.5985	16
Pentalene (10)	8	—	10.4556	1.0000	0.4707	0.0000	-1.4142	0.4707	179
— (107)	10	A 1	12.5130	0.9041	0.3357	-0.4110	-0.7102	0.7467	16
Thialene (108)	10	A 1	12.5412	0.7956	0.5293	-0.2570	-0.8338	0.7863	15
		B 2	12.605	—	0.460	-0.377	—	0.837	15
Isothialene (109)	10	A 1	12.479	—	0.444	-0.332	—	0.776	15
		B 2	12.563	—	0.376	-0.493	—	0.869	15
Azulene (11)	10	—	13.3635	0.8870	0.4773	-0.4004	-0.7376	0.8777	179
Benzo[<i>b</i>]thialene (110)	14	A 1	18.3847	0.8031	0.5137	-0.2325	-0.7708	0.7462	16
Benz[<i>f</i>]azulene	14	—	19.0838	0.8182	0.4219	-0.3165	-0.6535	0.7385	16

Dibenzo[b,f]thialene (111)	18	A 1	24.2044	0.7139	0.4388	-0.2956	-0.7084	0.7344	16
Dibenz[a,g]azulene	18	—	24.8591	0.6933	0.3500	-0.3652	-0.5650	0.7152	16
— (112)	10	A 1,C	12.0592	0.8411	0.5183	-0.2750	-0.7867	0.7933	16
2,3-Thienotropylium ^f (130)	10	A 1	13.9203	1.0378	0.8110	-0.3055	-0.4674	1.1165	16
3,4-Thienotropylium ^f	10	A 1	13.6930	1.0869	0.6105	-0.1133	-0.6218	0.7238	16
— (113)	12	A 1	14.9201	1.0000	0.0497	-0.3789	-0.6159	0.4286	16
Heptalene (12)	12	—	15.6182	1.0000	0.0000	-0.3111	-0.7046	0.3111	179
— (114)	12	A 1	14.2600	1.0000	0.1348	-0.4849	-0.5264	0.6197	16
Benzo[b]tropolthiazine ^f	16	A 1,C ^g	21.5049	0.8383	0.2482	-0.3819	-0.6015	0.6301	16
	16	A 1,C ^h	23.1156	0.8707	0.4832	-0.3819	-0.5512	0.8651	16
— (115)	10	A 1		1.0000	0.5312	-0.1880	-0.4768	0.3432	16
Dicyano-1,2,5-dithiinothiadiazole (43)	16	A 1,C	22.3421	0.9746	0.5348	-0.2999	-0.4163	0.8347	16
1,8-Naphthylene sulfide (117)	12	A 1	16.0223	0.8024	0.6979	-0.4267	-1.0000	1.1246	16
Acenaphthylene (14)	12	—	16.6189	0.8308	0.6375	-0.2846	-1.0000	0.9221	179
1-Thiaphenalene (118)	14	A 1	18.4971	1.0000	0.3595	-0.5417	-0.6870	1.2285	16
Pleiadiene (15)	14	—	19.1448	1.0000	0.2411	-0.4574	-0.7092	0.6985	179
— (120)	12	A 1	15.0925	0.6211	0.6180	-0.2697	-0.6275	0.8877	16
Sesquifulvalene (18)	12	—	15.9306	0.6180	0.5702	-0.4450	-0.4731	1.0152	179
— (121)	12	A 1	14.3449	0.6234	0.6180	-0.2630	-0.6275	0.8810	16
— (122)	10	B 2	12.3471	0.8764	0.3232	-0.6500	-1.0439	0.9732	16
— (123)	12	B 2	14.6094	0.8136	-0.0640	-0.3298	-0.8943	0.2658	16
— (124)	12	B 2	15.6363	0.6180	0.5785	-0.6180	-0.8636	1.1965	16
— (125)	14	B 2	17.7355	0.8597	0.0000	-0.2108	-1.0000	0.2108	16
— (126)	16	B 2	20.3409	0.4450	0.0736	-0.4450	-0.4710	0.5186	16

^a For explanations, see Section VI.

^b Anion.

^c Cation.

^d For parameters see footnote *b* of Table IX.

^e A tentative name.

^f See Fig. 12.

^g $\delta_N = 0.5$.

^h $\delta_N = 1.5$.

TABLE XIII
REACTIVITY INDICES (MODEL B3)

Compound	Position	q	F	S_e	S_r	S_{π}
Thiophene (26)	2	1.098	0.469	1.240	1.015	0.790
	3	1.102	0.392	1.069	0.844	0.618
Benzo[b]thiophene (27)	2	1.039	0.465	1.092	1.012	0.931
	3	1.120	0.438	1.297	0.974	0.650
	4	1.016	0.450	1.054	0.973	0.893
	5	1.028	0.400	0.931	0.850	0.769
	6	1.024	0.409	0.971	0.890	0.809
	7	1.022	0.429	1.005	0.843	0.924
Benzo[b]naphtho[2,3- <i>d</i>]-thiophene (34)	1	1.001	0.439	0.941	0.928	0.916
	2	1.032	0.404	0.989	0.878	0.768
	3	1.005	0.407	0.893	0.880	0.868
	4	1.032	0.429	1.034	0.923	0.812
	6	1.047	0.489	1.349	1.152	0.955
	7	1.009	0.456	1.080	1.030	0.981
	8	1.002	0.407	0.911	0.899	0.887
	9	1.011	0.407	0.949	0.899	0.850
	10	1.000	0.457	1.043	1.031	1.018
	11	1.003	0.500	1.206	1.157	1.108
Benzo[b]naphtho[2,1- <i>d</i>]-thiophene (35)	1	1.000	0.447	0.987	0.976	0.966
	2	1.010	0.407	0.931	0.889	0.848
	3	1.002	0.404	0.885	0.875	0.864
	4	1.008	0.451	1.035	0.993	0.951
	5	1.043	0.454	1.194	1.027	0.860
	6	0.997	0.440	0.951	0.940	0.930
	7	1.006	0.440	0.984	0.942	0.900
	8	1.029	0.402	0.960	0.866	0.773
	9	1.012	0.406	0.921	0.879	0.838
	10	1.027	0.429	1.019	0.925	0.831
Phenanthro[9,10- <i>c</i>]-thiophene (36)	1	1.098	0.519	1.510	1.207	0.904
	4	1.015	0.438	0.973	0.924	0.876
	5	1.002	0.406	0.895	0.882	0.870
	6	1.012	0.405	0.928	0.880	0.832
	7	1.003	0.438	0.939	0.927	0.915

of the $N \rightarrow V_1$ transition [$E(N \rightarrow V_1)$]. To facilitate comparisons, the same quantities for the parent systems are also included. In addition, Table XII presents the numbers of electrons in π -molecular orbitals (n), formula numbers used in this review, the names of the compounds (for those as yet unnamed in the literature either only the formula number is given or a name is tentatively proposed), and references to the model (see Section I, B, 3) used in the calculation. The compounds are ordered essentially in agreement with the classification adopted.

B. REACTIVITY INDICES

Table XIII presents the values of the π -electron density (q), free valence (F), and superdelocalizability (S_e , S_r , S_n) for the individual positions in benzothiophenes (Model B3).

Notes Added in Proof

Numerous theoretical and experimental investigations concerning sulfur-containing systems have been performed recently. Thiazoles, thiazolium ions, and their oxygen analogues were studied by means of NMR spectroscopy and MO calculations; unusually large C^{13} -H coupling constants were found.¹⁸³ The ESR spectra of dibenzothiophene radical anion and its isologs were interpreted and shortcomings of the Longuet-Higgins model critically analyzed.¹⁸⁴ The ESR spectra of the dibenzo-1,4-dithiin radical cation and related compounds were mentioned¹⁸⁵ (see also ref. 185a). New syntheses of thiapyrylium, 1-thianaphthylum,¹⁸⁶ 1,2-dithiolium,¹⁸⁷ and 1,3-dithiolium cations¹⁸⁸ and related ions were described. A close correlation was found between the pK_R values for several aromatic sulfur-containing cations and the corresponding HMO changes of the π -electron energy.¹⁸⁹ HMO calculations were performed for thioxanthone, benzthioxanthone, and

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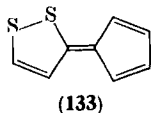
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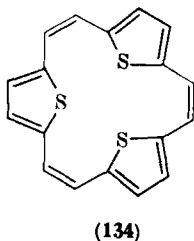
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a series of related compounds¹⁹⁰ and electronic spectral data and polarographic behavior were rationalized in terms of the theory. Electronic and NMR spectra and chemical reactivity of isothialene and related systems were studied.^{191, 192} A successful attempt was made to discuss the chemical shifts observed for isothialene in terms of the HMO π -electron densities.¹⁹³ A synthetic study concerning sulfur analogues (**133**) of sesquifulvalene was finished¹⁹⁴; HMO



characteristics of **133** seem to be favorable.¹⁹⁵ Quite a remarkable [18]-annulene trisulfide was prepared¹⁹⁶; the NMR spectrum of this compound shows two peaks of equal area in agreement with the equal number of the two types of protons in **134**. The result of an HMO



treatment of **134** suggests that it should have considerably higher delocalization energy per bond (0.304β) than [18]annulene (0.280β). Moreover, it seems that **134** will be more easily oxidized and less susceptible to reduction than [18]annulene.¹⁹⁵ Further theoretical and experimental papers on thioamides and thiohydrazides were pub-

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¹⁹⁴ A. Lüttringhaus, E. Futterer, and H. Prinzbach, *Tetrahedron Letters* No. **19**, 1209 (1963).

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lished.^{197, 198} The tautomerism of 1,3,4-thiadiazolylhydrazones was studied by means of UV spectroscopy and the results were successfully interpreted in terms of the MO theory.¹⁹⁹ The tendency of the thio-carbonyl group to give stronger mesomeric interaction with electron-donating groups than the carbonyl group was explained by means of the simple MO theory.²⁰⁰ In the same paper the technical aspects of the SC method used are discussed. The relationships between HMO and SC data (for the SC method, see ref. 200) were investigated carefully.²⁰¹ Generally speaking there is a correlation between the two sets of quantities. The excitation energies of the first bands and polarographic half-wave potentials of several dozens of sulfur-containing heterocycles were discussed in terms of the MO theory.^{202, 203} The electronic structures of some biologically important systems were calculated.^{204, 205} Experimental and theoretical aspects of the chemistry of sulfur compounds were treated in a symposium recently held in Czechoslovakia.²⁰⁶ Recently thiophene and dithienyls were studied by means of the SCF method.²⁰⁷

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Theoretical Studies of Physico-chemical Properties and Reactivity of Azines

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I. The Objective of the Theoretical Studies; Scope of the Review

The objective of theoretical studies in this field, as in others, is to reach such a state of knowledge of the interrelations between the structures and properties of chemical compounds that it would be possible to deduce, by theoretical means, correct information concerning various properties of a compound from the mere knowledge of its structure. In principle, an answer to this problem is provided by quantum mechanics and its application to the study of physical and chemical properties of chemical compounds. In practice, however, we

are restricted to the use of empirical and semi-empirical methods, hence the stated objective has to be approached by various studies which examine the relation of certain physical properties (e.g. spectral properties or geometrical structure of molecules) to appropriate theoretical quantities derived from an approximate solution of the Schroedinger equation for suitable models of the compounds studied. It is the purpose of these various studies, and there are quite a number of them dealing with the present topic, to provide a basis for the achievement of the goal defined at the outset.

The present article is an attempt to review those studies of pyridine-like heterocycles (mono-azines) and, to a lesser extent, their analogues and derivatives that have interpreted the behavior and estimated various physico-chemical properties of the compounds by the use of data calculated by the simplest version of the MO LCAO (molecular orbital, linear combination of atomic orbitals) method (both molecular orbital energies and expansion coefficients). In this review, attention is focused upon the use of the simple method because it has been applied to quite extensive sets of compounds and to the calculation of the most diverse properties. On the other hand, many fewer compounds and physico-chemical properties have been investigated by the more sophisticated methods. Such studies are referred to without being discussed in detail. In a couple of years, we believe, the extent of the applications of such methods will also be wide enough to warrant a detailed review.

Some aspects of this subject have been reviewed in detail recently and shall be only very briefly mentioned here.

II. Outline of Theoretical Methods and Characterization of Quantities Derived from Calculations

Several valence-bond (VB) treatments of heterocyclic compounds were reported in the thirties and forties.^{1, 2} The known difficulty in applying the VB method to complicated molecules has made an overwhelming majority of authors use the molecular orbital (MO) method. In most cases its simplest version, the naive MO LCAO method, has been used. This approximation differs from the well-known Hückel

¹ B. Pullman and A. Pullman, "Les théories électroniques de la chimie organique." Masson, Paris, 1952.

² G. W. Wheland, "Resonance in Organic Chemistry." Wiley, New York, 1955.

approximation only in the assignment of suitable empirically determined values of Coulomb and resonance integrals to orbitals of heteroatoms and to the carbon-heteroatom and heteroatom-heteroatom bonds; it therefore seems appropriate to call this method, according to Streitwieser's suggestion,³ the HMO method. Today the use of this method is so widespread that it is sufficient to refer the reader to some of the monographs which consider its technical aspects.¹⁻⁵

If the nitrogen atom's orbitals in a pyridine-like compound are assumed to be sp^2 hybridized, like carbon orbitals, the five $2s$ and $2p$ electrons obviously must be allotted to the individual orbitals as shown in Fig. 1. Overlap of the $2sp^2$ hybrid orbitals of the heteroatom with similar orbitals of the neighboring atoms results in the formation of σ -bonds; overlap of its $2p_z$ orbital with the $2p_z$ orbitals of other

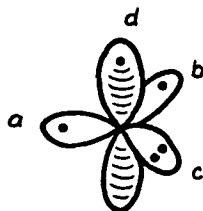


FIG. 1. Occupancy of $2sp^2$ (a, b, c) and $2p_z$ (d) nitrogen orbitals by electrons (●) in pyridine-like compounds. The orbital designated by c is non-bonding (the shape of the orbitals is somewhat distorted for clarity).

atoms in conjugation gives rise to delocalized π -bonds. The presence of the non-bonding atomic orbital occupied by two electrons confers basic properties on such compounds since overlap of this orbital with a $1s$ orbital of a proton can lead to the formation of an N-H bond; the number of electrons contributed by the nitrogen atom into conjugation is unchanged.

All that remains to be added is that the formulation of problems in the study of heterocyclic compounds requires that some $2p_z$ atomic orbitals and some bonds be assigned values of Coulomb and resonance integrals different from those for the carbon $2p_z$ orbital (α_C) and the

³ A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists." Wiley, New York, 1961.

⁴ C. A. Coulson, "Valence." Clarendon Press, Oxford, 1952.

⁵ R. Daudel, R. Lefebvre, and C. Moser, "Quantum Chemistry." Interscience, New York, 1959.

C—C bond (β_{CC})¹⁻⁵ (for a summary, see refs. 6 and 7). These values are reflected in the constants δ_X and ρ_{XY} in the expressions for the Coulomb (α_X) and resonance integrals (β_{XY}):

$$\alpha_X = \alpha_C + \delta_X \beta_{CC} \quad (1)$$

$$\beta_{XY} = \rho_{XY} \beta_{CC} \quad (2)$$

In the case of orbitals and bonds of conjugated hydrocarbons the constant δ_X vanishes and the constant ρ_{XY} is equal to one. In pyridine-like heterocyclic compounds the nitrogen $2p_z$ orbital is ascribed a δ_X value ranging from 0.2 to 1. Recent studies indicate that a value of 0.2–0.5 is preferable. The nitrogen atom in pyridinium compounds must be assigned a larger value, 1.5–2.0. For aromatic C—N and N—N bonds the ρ_{XY} value amounts to 0.9–1.0. In numerous studies the Coulomb and resonance integrals of other $2p_z$ orbitals and bonds were assigned the standard values (α_C , β_{CC}). In some studies, however, the inductive effect of the heteroatom on its neighbors has been taken into account by ascribing increased values of the Coulomb integrals to the orbitals of adjacent carbon atoms (for a summary, see ref. 8) or even to all atoms in the conjugated skeleton.⁹ In the first case, the orbitals adjacent to the orbital of the heteroatom are given a Coulomb integral value ranging from 5 to 10 percent of that of the heteroatom; in the second case this effect is considered to operate also at more distant atoms and the individual orbitals are assigned decreasing Coulomb integral values with increasing distance from the heteroatom as a geometrical series. In most studies the overlap integral has been neglected; the introduction of this integral has no appreciable effect on results obtained by the HMO method.¹⁰

Solution of the appropriate characteristic problem in π -electron approximation furnishes two kinds of quantities: π -molecular orbital energies, E_i , and molecular orbitals, ψ_i . The quantity E_i is usually expressed in the form of Eq. (3),

$$E_i = \alpha_C + k_i \beta_{CC} \quad (3)$$

⁶ J. Koutecký and R. Zahradník, *Collection Czech. Chem. Commun.* **28**, 2089 (1963).

⁷ R. Zahradník and C. Párkányi, *Collection Chem. Czech. Commun.* **30**, 353, (1965).

⁸ R. D. Brown, in "Current Trends in Heterocyclic Chemistry" (A. Albert, G. M. Badger, and C. W. Shoppee, eds.), p. 13. Butterworths, London, 1958, and references therein.

⁹ G. Coppens and J. Nasielski, *Tetrahedron* **18**, 507 (1962).

¹⁰ D. W. Davies, *Trans. Faraday Soc.* **51**, 449 (1955).

where β_{CC} (further simply β) is the energy unit (for definition, see above) and, according to convention, the quantity α_C (further simply α) is the zero of the energy scale. Molecular orbitals are expressed in terms of their expansion coefficients, c_{ij} (components of eigenvectors), which appear in Eq. (4),

$$\psi_i = \sum_{j=1}^n c_{ij} \varphi_j \quad (4)$$

where φ_j means a $2p_z$ atomic orbital; the sum is taken over all of the orbitals in conjugation (n).

In this connection a more detailed account will only be given of a method that permits calculation of HMO orbital energies of a model of a heterocycle without expanding the secular determinant from the knowledge of molecular orbital energies and expansion coefficients of the parent hydrocarbon.¹¹⁻¹⁵ Now that automatic computing machines are commonly used for quantum-chemical calculations we see the chief merit of the method in that it permits one to study the effect of empirical parameters on energy characteristics in a clear-cut and concise manner.

The values of the orbital energies, E , of the model of the heterocycle are obtained by solving an equation of type (5),

$$\sum_{i=1}^n \frac{c_{ij}^2}{E - k_i} = \frac{1}{\delta_X} \quad (5)$$

where c_{ij} is the expansion coefficient at the orbital φ_j in the i -th molecular orbital of the parent hydrocarbon whose energy is k_i (in β units) and δ_X is a constant characterizing the Coulomb integral of the heteroatom [Eq. (1)]; the sum is taken over all of the molecular orbitals (n).

The advantages offered by Eq. (5) can be demonstrated by an example. Suppose we want to know the orbital energies of a system which arises upon replacing the carbon $2p_z$ orbital in position 2 in naphthalene by a $2p_z$ orbital of a heteroatom, X. Substituting the

¹¹ J. Koutecký and A. Fingerland, *Dokl. Akad. Nauk SSSR* **125**, 841 (1959).

¹² M. J. S. Dewar, *Proc. Cambridge Phil. Soc.* **45**, 638 (1949).

¹³ J. Koutecký, *Trans. Faraday Soc.* **55**, 505 (1959).

¹⁴ A. Laforgue, *J. Chim. Phys.* **46**, 568 (1949).

¹⁵ The method in question is capable of solving considerably more general problems; in this place attention is restricted only to a special case for convenience.

known HMO values of c_{ij} and k_i for the naphthalene 2-position we obtain Eq. (5a).

$$\begin{aligned} & \frac{0.0532}{E-2.3028} + \frac{0.1809}{E-1.6180} + \frac{0.0301}{E-1.3028} + \frac{0.1667}{E-1.0000} + \frac{0.0691}{E-0.6180} \\ & + \frac{0.0691}{E+0.6180} + \frac{0.1667}{E+1.0000} + \frac{0.0301}{E+1.3028} + \frac{0.1809}{E+1.6180} \\ & + \frac{0.0532}{E+2.3028} = \frac{1}{\delta_X}. \end{aligned} \quad (5a)$$

A graphical solution of Eq. (5a) is advantageous. The polynomial on the left side is represented by a series of curves whose asymptotes are parallel to the ordinate axis (Fig. 2). Solutions of Eq. (5a) for a given

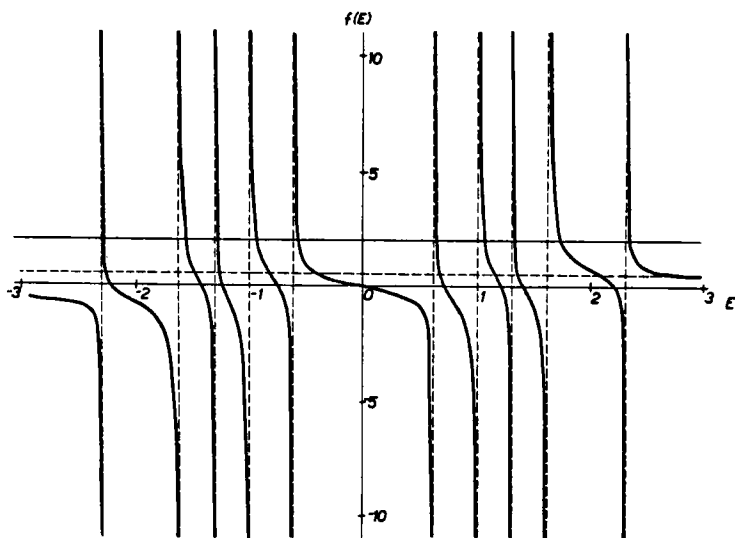


FIG. 2. Graphical solution of Eq. (5a) for $\delta_N = 0.5$ (—) and for $\delta_N = 2$ (----).

value of δ_X are given by the points of intersection of the curves shown in Fig. 2 with a straight line which cuts the ordinate axis at the point $1/\delta_X$ and is parallel to the abscissa axis. For the straight lines in Fig. 2, $\delta_X = 0.5$ and $\delta_X = 2.0$. The values of the orbital energies of models of quinoline and the quinolinium cation are found from the graph and checked easily; the sum of the orbital energies is equal to the trace of

the matrix of the corresponding characteristic problem,³ and the sum of their squares is equal to the sum of the squared matrix elements.¹⁶

Of the more exact methods, the limited configuration interaction (CI MO LCAO) method and the self-consistent field (SCF MO LCAO) method will be mentioned. In contrast to the HMO method, both of these explicitly take electron repulsion into account. The CI method is particularly valuable for the calculation of various physical properties, especially electronic spectra. A more detailed description is beyond the scope of the present review; the reader is referred to original papers [CI,¹⁷⁻²⁰ SCF,²¹⁻²³ and VESCF²⁴ (variable electronegativity)] and to various reviews and monographs.^{5, 25, 26}

III. Correlations Based on Molecular Orbital Energies

Before starting a discussion of the possibilities of correlating experimental data with theory, it seems appropriate to mention the interrelations between various theoretical energy characteristics.

Molecular orbital energies have been published⁶ for models of 73 hetero analogues derived from benzenoid hydrocarbons (Fig. 3) by replacing one carbon $2p_z$ orbital by the $2p_z$ orbital of a heteroatom. The calculations have been carried out for two values of δ_x (0.5 and 2.0) using the method described in Section II. Resultant energies of the four frontier orbitals, $N \rightarrow V_1$ transition energies, total π -electronic energies, and the differences in the total π -electronic energies of the heterocycles and the parent hydrocarbons (ΔW) for $\delta_x = 0.5$ are given in Section VI, A. Similar data for $\delta_x = 2$ are reported in ref. 6. The values of ΔW are approximately linearly dependent on the atom-localization energy of the position in the parent hydrocarbon in which

¹⁶ J. Koutecký, J. Čížek, and J. Paldus, personal communication (1960).

¹⁷ R. Pariser and R. G. Parr, *J. Chem. Phys.* **21**, 466 (1953).

¹⁸ R. Pariser and R. G. Parr, *J. Chem. Phys.* **21**, 767 (1953).

¹⁹ R. Pariser, *J. Chem. Phys.* **24**, 250 (1956).

²⁰ M. J. S. Dewar and H. C. Longuet-Higgins, *Proc. Phys. Soc. (London)* **67A**, 795 (1954).

²¹ C. C. J. Roothaan, *Rev. Mod. Phys.* **23**, 69 (1951).

²² J. A. Pople, *Trans. Faraday Soc.* **49**, 1375 (1953).

²³ J. A. Pople, *Proc. Phys. Soc. (London)* **68A**, 81 (1955).

²⁴ R. D. Brown and M. L. Heffernan, *Australian J. Chem.* **12**, 319, 330, 543, 554 (1959).

²⁵ R. G. Parr and F. O. Ellison, *Ann. Rev. Phys. Chem.* **6**, 171 (1955).

²⁶ H. C. Longuet-Higgins, *Advan. Chem. Phys.* **1**, 239 (1958).

the carbon orbital has been replaced by the orbital of the heteroatom (Fig. 4). The plot shows distinct regions corresponding to data for the individual classes of positions: class 0 (benzene-like positions),

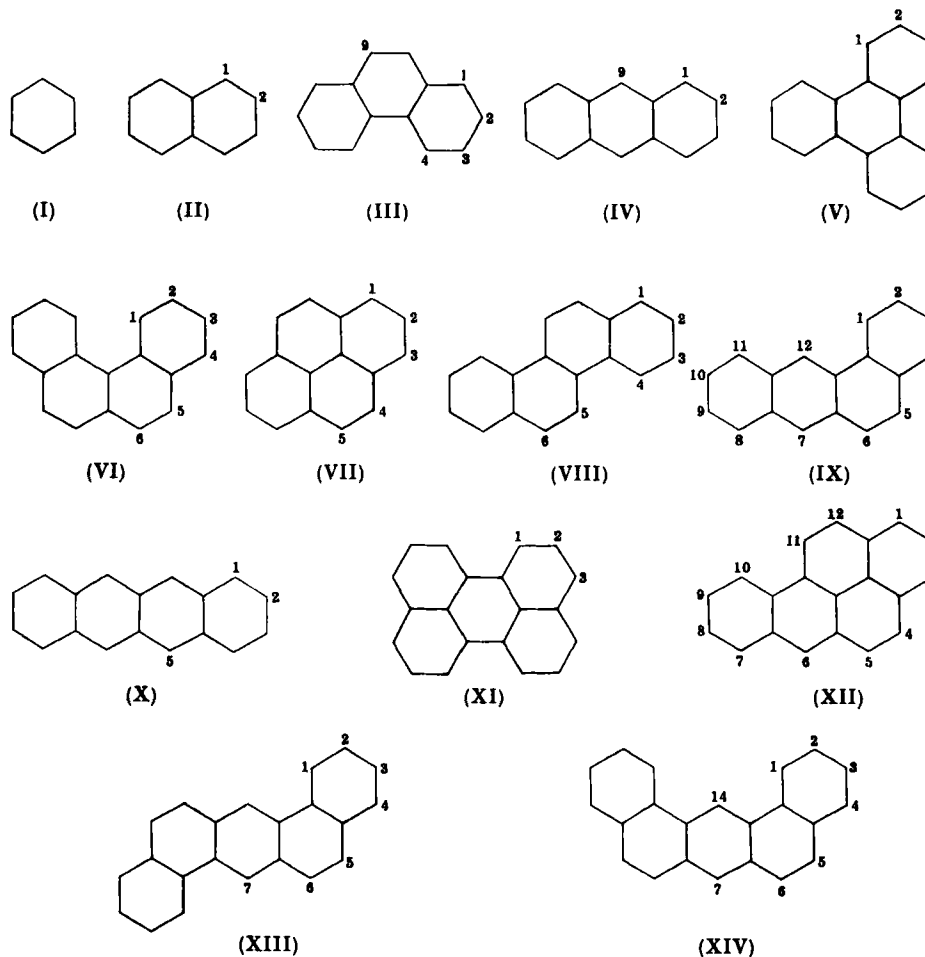


FIG. 3. Formulas of some analogues derived from benzenoid hydrocarbons.

class 1 (α -naphthalene-like positions), and class 2 (meso-anthracene-like positions). A more detailed discussion of this classification is given in ref. 27. Apparently, knowledge of the localization energy of a given

²⁷ J. Koutecký, R. Zahradník, and J. Čížek, *Trans. Faraday Soc.* **57**, 169 (1961).

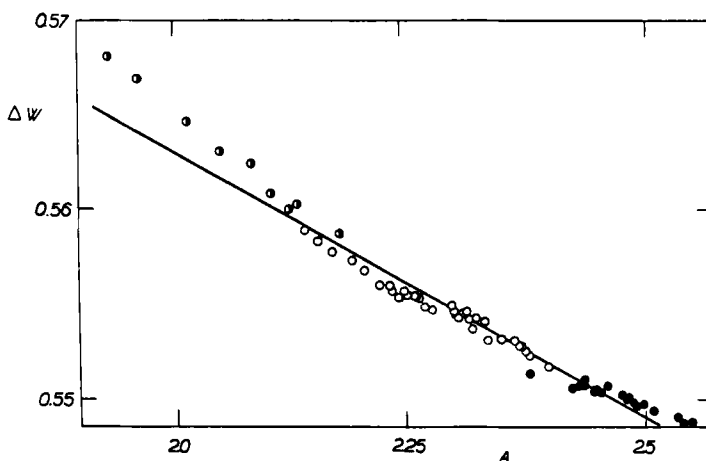


Fig. 4. Plot of ΔW versus A ,^a Designation (class of position²⁷): ● (0), ○ (1), and ◐ (2). (Reproduced by permission; from ref. 6).

position in a benzenoid hydrocarbon and of its π -electronic energy is sufficient to permit estimation of the π -electronic energy of the model of the corresponding heterocycle with reasonable precision. A similar relationship holds for the quantities computed for $\delta_X = 2$; the constants of these linear dependences are presented in Table I.

For a very high positive value of the Coulomb integral of the heteroatom, the difference between the π -electronic energy of the

TABLE I
REGRESSION LINE CONSTANTS (a, b ; $Y = aX + b$)^a

X^b	Y^b	a	b	r^c	n^d
A_i	ΔW (A)	-0.2884	3.4201	-0.9917	73
A_i	ΔW (B)	-0.0277	0.6184	-0.9774	72
$\Delta W(A)$	ΔW (B)	0.0968	0.2878	0.9930	72
$E(N \rightarrow V_1)$ (A)	$E(N \rightarrow V_1)$ (B)	1.3211	0.1905	0.9474	72

^a Reprinted by permission; from ref. 6.

^b The letters A and B in parentheses indicate the empirical parameter used in the HMO calculation (A: $\delta_N = 0.5$; B: $\delta_{N^+} = 2.0$). A_i denotes the atom localization energy.

^c Correlation coefficient.

^d Number of data points.

heterocycle and that of the parent hydrocarbon is equal to $2\delta_X - A_j$, A_j being the localization energy of the corresponding position in the parent hydrocarbon. An estimate of the effect of the values of δ_X upon ΔW is preferably gained by inspection of the plot of $(2\delta_X - \Delta W)$ against A_j ; it is seen that this quantity acquires values between zero ($\delta_X = 0$) and A_j ($\delta_X \rightarrow \infty$). The plots for several values of δ_X are shown in Fig. 5.

The quantity ΔW ($\delta_X = 0.5$) is a linear function of ΔW ($\delta_X = 2.0$) (Table I), as well as of the ΔW calculated for a model which allows for

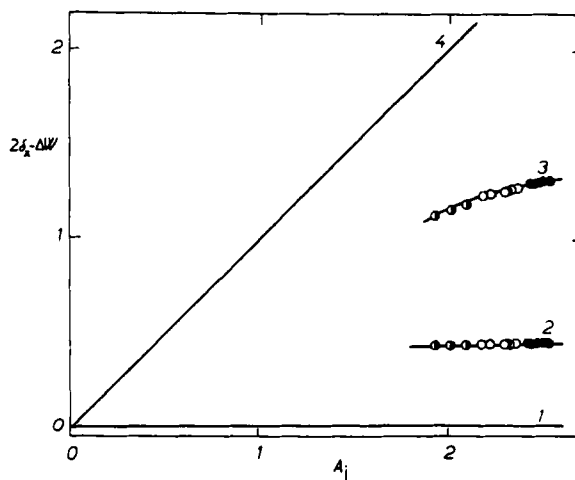


FIG. 5. Plot of $(2\delta_X - \Delta W)$ against A_j .⁶ Designation (δ_X): 1 (0), 2 (0.5), 3 (2.0), and 4 (∞); see also Fig. 4. (Reproduced by permission; from ref. 6.)

an inductive effect at all carbon orbitals of the conjugated skeleton.⁹ Surprisingly, the correlation between $E(N \rightarrow V_1)$ excitation energies for $\delta_X = 0.5$ and similar quantities for $\delta_X = 2.0$ is much less close (Table I). On the other hand $E(N \rightarrow V_1)$ ($\delta_X = 0.5$) is very close to a linear function of $E(N \rightarrow V_1)$ calculated for a model in which the inductive effect is allowed for.

The HMO method has been used to study models of all the aza analogues of pyridine, quinoline, isoquinoline, the monoazaanthracenes, and 1- and 9-azaphenanthrenes as well as of their derivatives such as aminopyridines and aminoquinolines.²⁸ Again their energy characteristics are correlated with those of the parent systems.

²⁸ R. Zahradník and J. Koutecký, unpublished results (1962).

Further, a systematic study of energy characteristics in a series of azines containing 2-4 nitrogen atoms in the molecule and of dihydroazines has been published.^{29, 30} A correlation was found between the calculated quantities and the experimental electronic excitation energies as well as the stabilities. Molecular diagrams were calculated for a selected group of representatives. Quite recently, various HMO and SCF characteristics have been calculated for a series of pyridine-like heterocycles and their amino derivatives.³¹

A. DELOCALIZATION ENERGIES

Delocalization energies (DE) are readily calculated from the total π -electronic energies. The following empirical relationship has been found³² between the experimental and theoretical delocalization energies of compounds of various types (see also ref.3):

$$DE_{exp} = 15.8 DE_{th} \quad (6)$$

In Eq. (6), DE_{exp} (cf. ref. 2) is given in kcal/mole and DE_{th} in β units. Data for non-alternant hydrocarbons and quinones have not been included. The data for pyridine² and quinoline^{2, 33} obey the equation satisfactorily. On the other hand, the theory predicts too high values for the diazines (pyridazine, pyrimidine, and pyrazine) which have recently been studied experimentally.³³

B. ELECTRONIC SPECTRA

Quantities which can be derived from the energies of frontier orbitals are discussed in Sections III, B, III, C, and III, D. Here we mean by frontier orbitals the two highest occupied and the two lowest free molecular orbitals. The occupied orbitals are usually bonding and the unoccupied ones anti-bonding. The correlation of experimental with calculated (HMO) data reported thus far are compiled in Table II. Linear relations of the type

$$y = ax + b \quad (7)$$

²⁹ Y. Akimoto, *Bull. Chem. Soc. Japan* **29**, 460 (1956).

³⁰ Y. Akimoto, *Bull. Chem. Soc. Japan* **29**, 553 (1956).

³¹ F. Peradejordi, personal communication (1963).

³² R. Zahradník, unpublished results (1962).

³³ J. Tjebbes, *Acta Chem. Scand.* **16**, 916 (1962).

are seen to exist between the stated quantities (y and x are the experimental and theoretical quantities, respectively, a and b are constants). In this connection it seems desirable to emphasize that in correlations with HMO data the constant b [cf. Eq. (7)] is generally different from zero and, in addition, can change as we pass from one structural type of organic compound to another.

The near-UV and visible absorption spectra of the compounds studied can exhibit two kinds of maxima³⁴: $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$. With

TABLE II
INTERRELATIONS OF EXPERIMENTAL (y) AND HMO
THEORETICAL QUANTITIES (x) BASED ON FRONTIER
ORBITAL ENERGIES ($y = ax + b$)^a

y	x^b
L_a band excitation energies	$E(N \rightarrow V_1)$
L_b and B_b excitation energies	$\bar{E}(N \rightarrow V)$
Excitation energy of the first absorption band of charge-transfer complexes (for a constant acceptor)	HOMO
Ionization potential (π -electronic)	HOMO
Electron affinity	LFMO
Polarographic cathodic half-wave potential	LFMO
Polarographic anodic half-wave potential	HOMO

^a For detailed information, see, e.g., refs. 1, 3, and 5.

^b For definition of $E(N \rightarrow V_1)$ and $\bar{E}(N \rightarrow V)$ see text; HOMO and LFMO are the energies of the highest occupied and lowest free π -molecular orbital, respectively.

pyridine and its polybenzo derivatives it is impossible to observe the $n \rightarrow \pi^*$ band under the usual conditions of measurement in solution,³⁵ since the excitation energy of the $n \rightarrow \pi^*$ electron transition is only slightly lower than that of the $\pi \rightarrow \pi^*$ transition and the former is

³⁴ F. A. Matsen, in "Chemical Applications of Spectroscopy" (A. Weissberger, ed.) p. 629. Interscience, New York, 1956; S. F. Mason, in "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Chapter 7, Vol. II. Academic Press, New York, 1963.

³⁵ H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy." Wiley, New York, 1962.

only weakly allowed and consequently of low intensity. The $n \rightarrow \pi^*$ bands of pyridine, quinoline, isoquinoline, and acridine have been identified with certainty only recently by measurements in hexane.³⁶ Addition of a small amount of a proton donor causes the disappearance of the $n \rightarrow \pi^*$ band and has a hyperchromic effect on the $\pi \rightarrow \pi^*$ transition. The agreement between the theoretical (HMO) and experimental excitation energies of the maxima of the $n \rightarrow \pi^*$ band is excellent.³⁶

Much more varied is the situation with the $\pi \rightarrow \pi^*$ transitions. It has proved possible to classify the individual absorption bands, at least formally, in a manner similar to that used for the absorption curves of benzenoid hydrocarbons, which they resemble strikingly.⁶ In Platt's classification,³⁷ the bands are called L_b , L_a , B_b , and B_a and correspond to Clar's³⁸ α , p , β , and β' bands in the spectra of benzenoid hydrocarbons.

Despite the similarity of the absorption curves of pyridine-like heterocycles to those of the parent hydrocarbons, the assignment of bands in the absorption spectra of the former is more difficult since the L_b bands, which lie mostly at longer wavelengths than the L_a bands, are allowed and consequently intense, unlike those in the latter.³⁹ Because of this fact, one feels sometimes uncertain about the character of the first intense band, which can be either the L_a or the L_b band. Spectral measurements at low temperatures (-180°) and measurements of fluorescence spectra in polarized light⁴⁰ have contributed to a more certain assignment of bands to individual electronic transitions. In general it can be said that the excitation energies of the maxima of L_b , L_a , and B_b bands of the heterocycles are very close to those of the corresponding bands of the parent hydrocarbons; the change in the intensity of the L_b band is the only specific feature inherent to pyridine-like compounds.

Table III summarizes experimental and theoretical data on the first three absorption bands (L_b , L_a , B_b) in the spectra of pyridine, quinoline, isoquinoline, acridine, and their benzo and dibenzo derivatives.

³⁶ G. Coppens, C. Gillet, J. Nasielski, and E. van der Donckt, *Spectrochim. Acta* **18**, 1441 (1962).

³⁷ J. R. Platt, *J. Chem. Phys.* **17**, 484 (1949).

³⁸ E. Clar, "Aromatische Kohlenwasserstoffe." Springer-Verlag, Berlin, 1952.

³⁹ Owing to molecular symmetry, the L_b band in hydrocarbons is usually only weakly allowed and has therefore low intensity.

⁴⁰ H. Zimmermann and N. Joop, *Z. Elektrochem.* **65**, 61 (1961).

TABLE III
SUMMARY OF SPECTRAL DATA^a

Compound	Form	Band ($\tilde{\nu}$ in cm^{-1})			$E(N \rightarrow V_1)^b$	$\bar{E}(N \rightarrow V)^b$	Reference (absorption spectrum)
		L_b	L_a	B_b			
Pyridine	Base	38.0	~ 50.5	—	1.841	2.004	41
	Acid	37.8	47.0	—	1.507	2.007	41
Quinoline	Base	32.0	35.4	42.1	1.230	1.638	41
	Acid	32.0	29.7	42.9	1.174	1.587	41
Isoquinoline	Base	31.5	35.7	45.9	1.222	1.610	40
	Acid	—	29.6	—	1.088	1.536	40
Benzo[<i>f</i>]quinoline	Base	29.1	34.5	37.3	1.184	1.369	42
Benz[<i>f</i>]isoquinoline	Base	28.8	34.2	40.3	1.209	1.365	43
Benz[<i>h</i>]isoquinoline	Base	29.2	33.9	40.8	1.199	1.368	43
Phenanthridine	Base	28.9	33.3	40.3	1.201	1.372	42
Benzo[<i>g</i>]quinoline	Base	—	25.7	39.5	0.823	1.372	44
Benz[<i>g</i>]isoquinoline	Base	—	25.5	40.0	0.823	1.368	44
Acridine	Base	28.2	26.0	39.5	0.840	1.419	44, 41
	Acid	28.3	23.3	38.7	0.916	1.458	44, 41
Dibenzo[<i>f,h</i>]quinoline	Base	29.2	35.7	38.9	1.297	1.352	44

Naphtho[1,2- <i>f</i>]quinoline	Base	26.7	31.2	35.7	1.107	1.222	44
Naphtho[2,1- <i>f</i>]quinoline	Base	27.6	30.3	38.2	1.026	1.302	44
Benzo[<i>c</i>]phenanthridine	Base	27.9	30.7	38.2	1.027	1.291	45
Benzo[<i>i</i>]phenanthridine	Base	27.9	30.7	37.6	1.035	1.310	45
Benz[<i>a</i>]acridine	Base	25.8	(27.4) ^c	34.7	0.913	1.172	44
	Acid	—	—	34.3	0.903	1.199	44
Naphtho[1,2- <i>g</i>]quinoline	Base	25.8	(27.2) ^c	34.5	0.897	1.164	44
	Acid	25.5	—	—	0.830	1.129	44
Benz[<i>c</i>]acridine	Base	25.8	—	34.7	0.898	1.169	44
	Acid	—	—	34.3	0.824	1.177	44
Benz[<i>b</i>]acridine	Base	25.4	19.7	35.7	0.598	1.078	41
	Acid	25.2	17.1	35.0	0.642	1.118	41
Dibenz[<i>a,c</i>]acridine	Base	26.8	(29.4) ^c	35.2	0.994	1.213	41
	Acid	24.8	—	33.8	—	1.186	41
Dibenz[<i>a,h</i>]acridine	Base	25.2	(29.5) ^c	33.4	0.931	1.154	41
	Acid	23.3	—	31.9	0.821	1.106	41
Dibenz[<i>a,j</i>]acridine	Base	25.0	(29.2) ^c	34.0	0.990	1.113	41
	Acid	23.3	—	33.1	0.832	1.129	41
Dibenz[<i>c,h</i>]acridine	Base	25.3	(29.0) ^c	32.9	0.972	1.104	41
	Acid	23.3	—	32.1	0.871	1.059	41

^a Reprinted by permission; from ref. 6.

^b $\delta_N = 0.5$.

^c A tentative assignment.

Experimental data were taken from refs. 40–45 and theoretical data from ref. 6. Excitation energies of the L_a bands exhibit a significant correlation with $N \rightarrow V_1$ transition energies [$E(N \rightarrow V_1)$] and those of the L_b and B_b bands with the mean of the excitation energies of transitions $1 \rightarrow 2'$ and $2 \rightarrow 1'$, $^{46} \bar{E}(N \rightarrow V)$. In the case of the data on the L_a bands that are marked with footnote *c* in Table III, the correlation

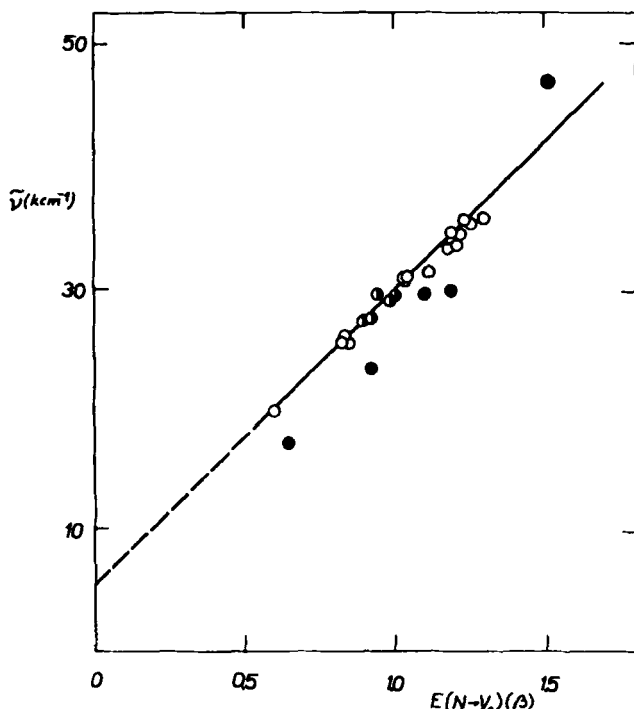


FIG. 6. Excitation energies of L_a bands ($\bar{\nu}$) plotted against $E(N \rightarrow V_1)$. Designation: free bases (\circ), conjugated acids (\bullet), and the positions of the maxima estimated tentatively (\odot). (Reproduced by permission; from ref. 6.)

⁴¹ V. Zanker and P. Schmid, *Chem. Ber.* **92**, 615 (1959).

⁴² R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds." Wiley, New York, and Chapman and Hall, London, 1951.

⁴³ G. Coppens, *Bull. Soc. Chim. Belges* **69**, 413 (1960).

⁴⁴ G. M. Badger, R. S. Pearce, and R. Pettit, *J. Chem. Soc.* 3199 (1951).

⁴⁵ G. M. Badger and J. H. Seidler, *J. Chem. Soc.* 2329 (1954).

⁴⁶ Occupied orbitals are numbered starting with the highest occupied orbital (1, 2, ...) and vacant orbitals starting with the lowest free orbital (1', 2' ...).

between experimental and theoretical data has been used inversely for a tentative assignment since the relevant regions in the spectra of these compounds contain numerous intense peaks and are not analyzed easily. Figures 6 and 7 present the relations studied; Table IV

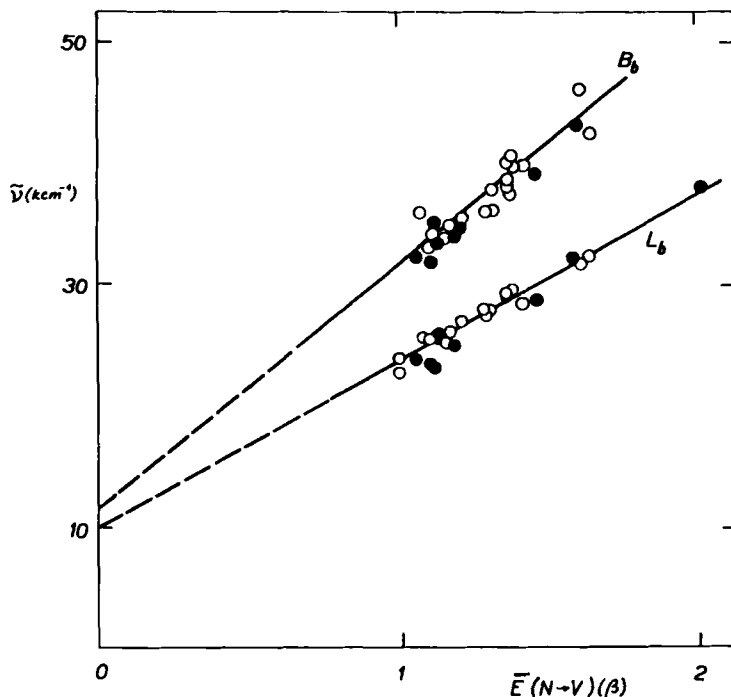


FIG. 7. Excitation energies of L_b and B_b bands ($\bar{\nu}$) plotted against $\bar{E}(N \rightarrow V)$. Designation: free bases (\circ) and conjugated acids (\bullet); the regression lines are those of free bases. (Reproduced by permission; from ref. 6.)

gives the values of regression line constants. For the sake of comparison, Table IV includes data for benzenoid hydrocarbons; both classes of compounds obviously behave similarly.

Much effort has been devoted to the study of the electronic spectra of aza analogues of pyridine (pyridazine, pyrimidine, pyrazine, sym. (1,3,5-)triazine, and sym. (1,2,4,5-)tetrazine) as well as of derivatives of all these compounds. Most of these absorption spectra are similar to those of the parent compounds, except for a band corresponding to the $n \rightarrow \pi^*$ transition which appears in the long-wavelength

TABLE IV

CONSTANTS OF REGRESSION LINES (a, b)^a OF THE RELATIONS
BETWEEN EXPERIMENTAL AND HMO THEORETICAL DATA^b

Com- pounds ^c	y	x ^d	a	b	r ^e	n ^f	Ref. ^g
P	$\tilde{\nu}(\text{kcm}^{-1})$, L_a band	$E(N \rightarrow V_1)$	24.031	5.584	0.994	22	6
H			19.207	10.234	0.982	44	47
P	$\tilde{\nu}(\text{kcm}^{-1})$, L_b band	$\bar{E}(N \rightarrow V)$	13.774	9.882	0.989	21	6
H			15.517	7.479	0.982	27	48
P	$\tilde{\nu}(\text{kcm}^{-1})$, B_b band	$\bar{E}(N \rightarrow V)$	20.254	11.431	0.928	22	6
H			23.763	11.638	0.965	40	48
P	$\tilde{\nu}(\text{kcm}^{-1})$, 1st ChT band ^h	HOMO	22.370	6.386	0.951	9	50
H			26.275	2.202	0.961	20	51
P	$\tilde{\nu}(\text{kcm}^{-1})$, 1st ChT band ⁱ	HOMO	23.204	8.301	0.959	7	50
H			25.824	5.249	0.984	13	51
P	$E_{1/2}(V)$, half-wave potentials ^j	LFMO	2.127	-0.555	0.986	6	52
H			2.405	-0.420	0.965	40	52

^a $y = ax + b$.

^b Cf. Table II.

^c P and H stand for pyridine-like heterocycles and benzenoid hydrocarbons, respectively.

^d In β -units; $\delta_N = 0.5$.

^e Correlation coefficient.

^f Number of compounds.

^g For additional references, see ref. 3.

^h Complexes with tetracyanoethylene.

ⁱ Complexes with chloranil.

^j Cathodic waves; for experimental conditions see Table VI.

⁴⁷ J. Koutecký, J. Paldus, and R. Zahradník, *J. Chem. Phys.* **36**, 3129 (1962).

⁴⁸ R. Zahradník, calculated for this review; see also ref. 49.

⁴⁹ J. Koutecký, J. Paldus, and V. Vitek, *Collection Czech. Chem. Commun.* **28**, 1468 (1963).

⁵⁰ M. Nepraš and R. Zahradník, *Collection Czech. Chem. Commun.* **29**, 1555 (1964).

⁵¹ M. Nepraš and R. Zahradník, *Collection Czech. Chem. Commun.* **29**, 1545 (1964).

⁵² C. Párkányi and R. Zahradník, *Abhan. deut. Akad. Wiss. (Berlin)* **363** (1964); *Bull. Soc. Chim. Belg.* **73**, 57 (1964); cf. ref. 172 in the "Notes Added in Proof."

region of the spectra of polyaza compounds. This is due to the decrease in the energies of both the highest occupied and lowest free molecular orbitals, whereas the energy of the non-bonding atomic orbital, n , remains virtually constant. There is no difficulty in characterizing the $n \rightarrow \pi^*$ transition.³⁴ This topic has recently been reviewed exhaustively by Mason,⁵³ who studied the electronic spectra of these compounds intensively (see, e.g., ref. 54 and especially ref. 55). In addition, the spectral studies of these compounds have been successfully reviewed by Jaffé and Orchin⁵⁵; their treatise also includes diazanaphthalenes and various other aza aromatics. A very detailed discussion of various aspects of the electronic spectra of mono- and di-azaphenanthrenes has been published recently.⁵⁶

It has been found³² with a number of diaza analogues of benzenoid hydrocarbons and with derivatives of monoaza analogues that the data for the three main bands lie in the vicinity of the regression lines for monoaza heterocycles. For 16 mono- and poly-aza heterocycles, $n \rightarrow \pi^*$ excitation energies have been calculated using the one-electron approximation^{56a}; the agreement with experiment is satisfactory. In the same paper, the effect of substituents on the $n \rightarrow \pi^*$ band excitation energies is discussed. Further, $\pi \rightarrow \pi^*$ excitation energies have been calculated for a set of amino derivatives of quinoline and isoquinoline.⁵⁷

Although the method of Pariser and Parr (CI MO LCAO) has been used to calculate the excitation energies of $n \rightarrow \pi^*$ ^{68, 73, 81, 82} and $\pi \rightarrow \pi^*$ transitions in quite a number of papers,^{18, 58-83a} the selection

⁵³ S. F. Mason, *Quart. Rev. (London)* **15**, 287 (1961).

⁵⁴ S. F. Mason, *J. Chem. Soc.* 1204, 1240, 1247, 1263, 1269 (1959).

⁵⁵ S. F. Mason, *J. Chem. Soc.* 493 (1962).

⁵⁶ H. Gropper and F. Dörr, *Ber. Bunsenges. Phys. Chem.* **67**, 46 (1963).

^{56a} L. Goodman and R. W. Harrell, *J. Chem. Phys.* **30**, 1131 (1959).

⁵⁷ S. Basu, *J. Chim. Phys.* **56**, 981 (1959).

⁵⁸ R. McWeeny and T. E. Peacock, *Proc. Phys. Soc. (London)* **70A**, 41 (1957).

⁵⁹ R. McWeeny, *Proc. Phys. Soc. (London)* **70A**, 593 (1957).

⁶⁰ T. E. Peacock, *Proc. Phys. Soc. (London)* **70A**, 654 (1957).

⁶¹ N. Mataga and K. Nishimoto, *Z. Physik. Chem. (Frankfurt)* **13**, 140 (1957).

⁶² K. Nishimoto and N. Mataga, *Z. Physik. Chem. (Frankfurt)* **12**, 335 (1957).

⁶³ L. Paolini, *Gazz. Chim. Ital.* **87**, 313 (1957).

⁶⁴ M. J. S. Dewar and L. Paolini, *Trans. Faraday Soc.* **53**, 261 (1957).

⁶⁵ G. Favini and S. Carrà, *Gazz. Chim. Ital.* **87**, 1367 (1957).

⁶⁶ N. Mataga, *Bull. Chem. Soc. Japan* **31**, 453 (1958).

⁶⁷ N. Mataga, *Bull. Chem. Soc. Japan* **31**, 463 (1958).

⁶⁸ T. Anno, *J. Chem. Phys.* **29**, 1161 (1958).

of the compounds studied has been rather limited; in addition to pyridine,^{18, 58, 59, 61, 62, 69, 70, 75, 76, 80} quinoline,^{60, 71} isoquinoline,^{60, 71} acridine,⁶⁶ the diazines,^{18, 58, 59, 61, 62, 66, 69, 76, 77} a triazine,^{18, 61, 62, 69, 81} and a tetrazine,^{63, 69} attention has only been paid to chloro derivatives of aza heterocycles and azines,^{78, 79} the quinolininium cation,⁷⁴ azobenzene,⁶⁰ melamine,⁶⁴ and naphthyridines.^{83a} Two studies devoted to the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions in aza heterocyclic compounds represent a further development of the Pariser and Parr method.^{68, 73}

In summary it can be said that the agreement of values of the experimental and theoretical excitation energies is fair.

C. IONIZATION POTENTIALS AND CHARGE-TRANSFER SPECTRA

With heterocyclic compounds the determination of the first ionization potential, corresponding to excitation of an electron from the highest occupied π -molecular orbital, is complicated considerably by the fact that excitation from an n -orbital often precedes that from a π -orbital; the difference in the energies of these two orbitals is small in the case of pyridine and pyrazine.⁸³ There are two pieces of evidence which indicate that for pyridine-like heterocycles and their aza analogues the excitation in question is from an n -orbital: first, the parallelism between ionization potentials and basicities (in agreement with an SCF treatment^{84-86a}), and, second, the very small differences

⁶⁰ J. N. Murrell, *Mol. Phys.* **1**, 384 (1958).

⁷⁰ N. Mataga and S. Tsuno, *Naturwissenschaften* **45**, 333 (1958).

⁷¹ N. Mataga, *Bull. Chem. Soc. Japan* **31**, 459 (1958).

⁷² N. Mataga, *Bull. Chem. Soc. Japan* **31**, 463 (1958).

⁷³ T. Anno, *J. Chem. Phys.* **29**, 1170 (1958).

⁷⁴ T. E. Peacock, *J. Chem. Soc.* 3645 (1959).

⁷⁵ S. Mataga and N. Mataga, *Z. Physik. Chem. (Frankfurt)* **19**, 231 (1959).

⁷⁶ S. Mataga and N. Mataga, *Bull. Chem. Soc. Japan* **32**, 521 (1959).

⁷⁷ S. Mataga and N. Mataga, *Bull. Chem. Soc. Japan* **32**, 511 (1959).

⁷⁸ G. Favini and M. Simonetta, *Gazz. Chim. Ital.* **89**, 2222 (1959).

⁷⁹ G. Favini and M. Simonetta, *Gazz. Chim. Ital.* **90**, 363, 369 (1960).

⁸⁰ T. E. Peacock, *J. Chem. Soc.* 1946 (1960).

⁸¹ J. S. Brinen and L. Goodman, *J. Chem. Phys.* **31**, 482 (1959).

⁸² D. R. Kearns and M. A. El-Bayoumi, *J. Chem. Phys.* **38**, 1508 (1963).

⁸³ K. Maeda, *Bull. Chem. Soc. Japan* **31**, 890 (1958).

^{83a} T. E. Peacock, *J. Chem. Soc.* 2308 (1959).

⁸⁴ T. Nakajima and B. Pullman, *Bull. Soc. Chim. France* 1502 (1958).

⁸⁵ T. Nakajima and A. Pullman, *Compt. Rend.* **246**, 1047 (1958).

^{86a} T. Nakajima and A. Pullman, *J. Chim. Phys.* **55**, 793 (1958).

in the values of the ionization potentials of pyridines and methylpyridines⁸⁶ (cf. ref. 87).

The lack of direct ionization potential measurements can be partly circumvented by taking recourse to the excitation energies of the first charge-transfer bands of complexes of these compounds with tetracyanoethylene and chloranil,⁵¹ which have been measured for a number

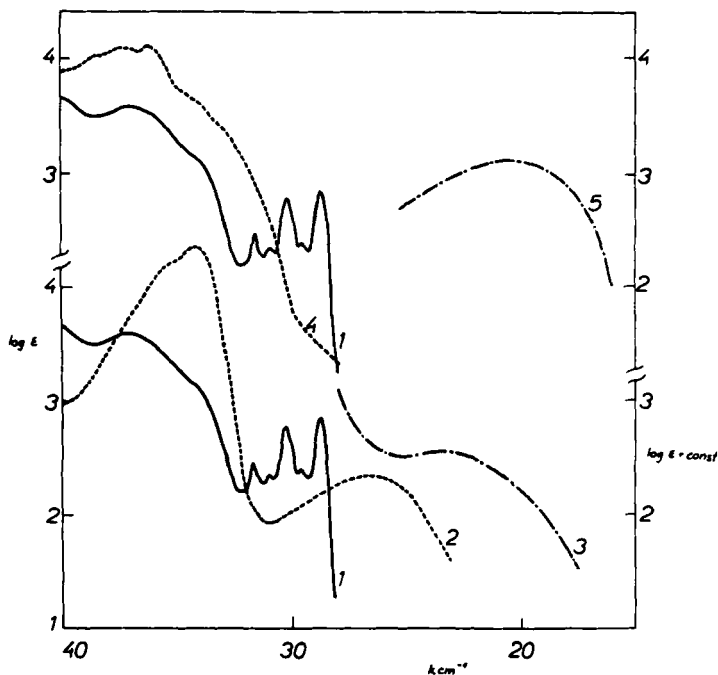


FIG. 8. Absorption spectra⁹⁰: 1, benzo[f]quinoline; 2, chloranil; 3, the complex of 1 + 2; 4, tetracyanoethylene; and 5, the complex of 1 + 4.

of heterocyclic compounds. The interrelation between these energies and ionization potentials has been proved empirically many times.⁸⁸ In the ground state of a π - π charge-transfer complex there is partial electron transfer from the highest occupied π -molecular orbital of the

⁸⁶ K. Higasi, I. Omura, and H. Baba, *J. Chem. Phys.* **24**, 623 (1956).

⁸⁷ I. Omura, H. Baba, K. Higasi, and Y. Kanaoka, *Bull. Chem. Soc. Japan* **30**, 633 (1957).

⁸⁸ G. Briegleb, "Elektronen-Donator-Acceptor Komplexe." Springer-Verlag, Berlin, 1961.

donor (HOMO) to the lowest free π -molecular orbital of the acceptor resulting in a lowering of the total π -electronic energy.⁸⁹ In the excited state this transfer is virtually complete. Figure 8 provides examples of absorption curves of charge-transfer complexes.

The complexes of heterocyclic compounds with acceptors of the type mentioned, like similar complexes of benzenoid hydrocarbons, yield a linear plot of energies of the first charge-transfer bands against HOMO energies of the donors.⁵⁰ Table V presents experimental and theoretical data for complexes of pyridine-like heterocycles with

TABLE V
ENERGIES OF THE MAXIMA OF FIRST CHARGE-TRANSFER BAND ($\tilde{\nu}$)⁵⁰

Donor	HOMO of donor, β^a	$\tilde{\nu}(\text{kcm}^{-1})$	
		A ^b	B ^c
Quinoline	0.703	22.0	—
Acridine	0.514	18.2	20.6
Benzo[<i>f</i>]quinoline	0.648	20.9	23.3
Benz[<i>f</i>]isoquinoline	0.606	20.5	—
Benzo[<i>h</i>]quinoline	0.623	20.6	23.0
Phenanthridine	0.683	20.9	23.6
Benzo[<i>g</i>]quinoline	0.459	15.6	18.0
Benz[<i>a</i>]acridine	0.553	18.8	21.5
Benz[<i>c</i>]acridine	0.523	18.8	21.0

^a $\delta_N = 0.5$.

^b Complexes with tetracyanoethylene.

^c Complexes with chloranil.

tetracyanoethylene and chloranil. The constants of regression lines of the plots are given in Table IV. Excitation energies for pyridine-like heterocycles are always higher than those for the corresponding parent hydrocarbons, in agreement with the finding that HOMO energies are always lower in models of heterocycles.

Data presented in Table IV make it clear that the correlations are sufficiently close. There is apparent similarity between the behavior of the heterocyclic compounds and benzenoid hydrocarbons which supports the claims^{50, 90} that these complexes are of the π - π type.

⁸⁹ R. S. Mulliken, *J. Am. Chem. Soc.* **72**, 600 (1950).

⁹⁰ M. Nepřaš, personal communication (1963).

The long-wavelength absorption bands exhibited by solutions of methiodides of aza analogues of benzenoid hydrocarbons have been attributed to the presence of charge-transfer complexes.⁹¹ There is a correlation between the excitation energies of the bands and the calculated electron affinity of the cations, in agreement with the delocalized rather than the localized model of the excited state in the charge-transfer complex.⁹¹

D. POLAROGRAPHIC HALF-WAVE POTENTIALS^{91a}

Like benzenoid hydrocarbons, pyridine-like heterocycles give well-developed two-electron waves on reduction at the dropping mercury electrode. The latter are polarographically much more reducible than the former. This can be explained easily in terms of the HMO theory: It is assumed (cf. ref. 3) that the value of the half-wave potential is determined essentially by the energy of the lowest free π -molecular orbital (LFMO) of the compound to be reduced, and for models of hetero analogues this quantity is always lower than that for the parent hydrocarbons. Introduction of an additional heteroatom into the molecule leads to a further enhancement of the ease of polarographic reducibility.⁹⁵ On the other hand, anodic oxidation of the heterocyclic compounds is so much more difficult in comparison with benzenoid hydrocarbons that they are not oxidizable under the usual polarographic conditions. An explanation in terms of the HMO theory is obvious.

Table VI summarizes half-wave potentials of cathodic waves. These values are linearly dependent on the energies of lowest free π -molecular orbitals. The correlation is just about as close (Table IV) as those for analogous quantities with benzenoid and other hydrocarbons and derivatives of benzenoid hydrocarbons.

At present it is difficult to decide whether the correlation found has a deeper physical meaning or whether it is only a mediated second-hand parallelism. In addition, owing to the limited solubility of these

⁹¹ S. F. Mason, *J. Chem. Soc.* 2437 (1960).

^{91a} J. Volke, in "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Chapter 6, Vol. I. Academic Press, New York, 1963.

⁹² M. K. Shchennikova and I. A. Korshunov, *Zh. Fiz. Khim.* **22**, 503 (1948).

⁹³ V. Zanker and H. Schnith, *Chem. Ber.* **92**, 2210 (1959).

⁹⁴ C. Párkányi and R. Zahradník, *Bull. Soc. Chem. Belges* **73**, 57 (1964).

⁹⁵ M. Březina and P. Zuman, "Polarography in Medicine, Biochemistry, and Pharmacy." Interscience, New York, 1958.

compounds, it is hardly possible to devise an experimental arrangement that would guarantee fully defined conditions. In spite of the vagueness and difficulties mentioned, the linear relationship found can still be used for interpolations.

TABLE VI
HALF-WAVE REDUCTION POTENTIALS OF MONOAZA-HETEROCYCLES

Compound	$E_{1/2}(V)$				k_{-1}^c
	A ^a		B ^b		
	1st wave	2nd wave	1st wave	2nd wave	
Pyridine	-2.07	—	-2.36 ^d	—	-0.841
Quinoline	-1.69	—	[-1.95]	—	-0.527
Isoquinoline	-1.84	—	—	—	-0.576
Acridine	-1.24	—	-1.20[-1.10]	-1.65[-1.70]	-0.325
Phenanthridine	-1.64	—	—	—	-0.518
Benzo[<i>f</i>]quinoline	-1.70	—	-2.05 ^d	-2.29 ^d	-0.536
Benz[<i>f</i>]isoquinoline	-1.41	-1.78 ^e	—	—	-0.603
Benz[<i>a</i>]acridine	—	—	-1.30	-1.60	-0.360
Benz[<i>b</i>]acridine	—	—	-0.90[-0.80]	-1.40[-1.40]	-0.227
Benz[<i>c</i>]acridine	—	—	-1.30	-1.60	-0.375
Dibenz[<i>a,c</i>]acridine	—	—	-1.45	— ^e	-0.411
Dibenz[<i>a,j</i>]acridine	—	—	-1.45	— ^e	-0.395
Dibenz[<i>c,h</i>]acridine	—	— ^t	-1.65	— ^e	-0.423
Dibenz[<i>b,h</i>]acridine	—	—	-1.35	-1.55	-0.268

^a 0.05M (C₂H₅)₄NI in dimethylformamide (5% H₂O). $E_{1/2}$ measured against a mercury pool.⁹⁴

^b 0.01M KOH (values in parentheses: 0.01M LiBr). $E_{1/2}$ measured against a SCE.⁹³

^c Energy of the lowest free π -molecular orbital.⁶

^d For electrolyte composition with pyridine and benzo[*f*]quinoline, see ref. 92; the quinoline $E_{1/2}$ value has been used to calculate their $E_{1/2}$ values against SCE.

^e This wave taken into the correlation.

IV. Correlations Based on Expansion Coefficients of π -Molecular Orbitals

A. DIPOLE MOMENTS

A calculation of the theoretical π -electron contribution to the dipole moment is a very simple matter provided the theoretical π -

electron densities and the molecular geometry are known.^{1, 3, 5} If the empirical parameters are adjusted, even the HMO method leads to a good agreement of theoretical with experimental values for pyridine^{5, 96} and the three diazines.⁹⁶ Much more satisfactory for the calculations of π -electron distribution is the SCF MO LCAO method; a satisfactory agreement of theoretical with experimental data has been obtained⁹⁷ with pyridine (see also ref. 98), pyridazine, pyrimidine, quinoline, isoquinoline, and acridine. With the exception of acridine, the dipole moments of these compounds were calculated earlier with similar success,⁹⁹ and the authors pointed out the relatively high value of the lone-pair dipole moment of the nitrogen atom, which is higher by some 1.33 D than the dipole moment of the C—H bond. In view of the rather high contribution of the σ -moment to the total dipole moment, the accurately measured dipole moment of pyridine was used to calculate the σ -moment, and the resultant value was used in the calculations of dipole moments of other compounds.

B. RADIOFREQUENCY SPECTROSCOPIES

The study of nuclear quadrupole resonance (NQR) frequencies of nitrogen-containing heterocyclic compounds is difficult but nevertheless possible.¹⁰⁰ More accessible are the investigations of chloro derivatives of pyridine and quinoline¹⁰⁰ and a series of chloropyrimidines.¹⁰¹ Through the use of the halogen atom this method makes it possible to estimate experimental π -electron densities in the individual positions of the parent heterocyclic skeleton. The results of these studies and the problems in NQR spectroscopy in general are discussed in a very fine recent review¹⁰⁰ (see also ref. 102).

The ESR method has thus far been applied only to a few radical anions derived from aza analogues of benzene, naphthalene, and

⁹⁶ L. E. Orgel, T. L. Cottrell, W. Dick, and L. E. Sutton, *Trans. Faraday Soc.* **47**, 113 (1951).

⁹⁷ A. T. Amos and G. G. Hall, *Mol. Phys.* **4**, 25 (1961).

⁹⁸ S. Odier and M. Roux, *J. Chim. Phys.* **50**, 141 (1953).

⁹⁹ H. F. Harnika and A. M. Liquori, *Mol. Phys.* **1**, 9 (1958).

¹⁰⁰ E. A. C. Lucken, in "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Chapter 8, Vol. II. Academic Press, New York, 1963.

¹⁰¹ H. O. Hooper and P. J. Bray, *J. Chem. Phys.* **30**, 957 (1959).

¹⁰² M. J. S. Dewar and E. A. C. Lucken, *Chem. Soc. (London), Spec. Publ. No. 12*, 223, (1958).

anthracene¹⁰³⁻¹⁰⁷ and from pyridazine and pyrazine¹⁰⁸ (see also ref. 109). The attempted preparations of pyridine and pyrimidine radical anions failed because of the high reactivity of these radicals. Several radical cations derived from aza heterocyclic compounds have been investigated.¹¹⁰ In general, the HMO calculations give satisfactory results for hfs (hyperfine splitting) constants. An authoritative review of both the theoretical and experimental aspects of the results obtained so far appeared recently.¹⁰⁸

Even though at present various obstacles prevent a more extensive application of NMR spectroscopy to the study of π -electron distribution, it seems that it will be possible to make use of the interrelation between the magnitude of the chemical shift of a proton attached at a certain position and the π -electron density at that position. Among the studies so far published attention should be drawn to the papers dealing with pyridine,¹¹¹⁻¹¹² substituted pyridines,¹¹³ and pyrimidine and its derivatives.¹¹⁴ Table VII presents data (taken from ref. 112) on experimental and theoretical π -electron densities in pyridine and the pyridinium cation. The NMR spectra of some azines are briefly discussed by White.^{114a}

C. BOND LENGTHS

The studies in this field are based on Coulson's well-known finding¹¹⁶ that there is a correlation between bond length and mobile bond order.

¹⁰³ J. C. M. Henning and C. de Waard, *J. Chem. Phys.* **35**, 2258 (1961).

¹⁰⁴ R. L. Ward, *J. Am. Chem. Soc.* **83**, 3623 (1961).

¹⁰⁵ A. Carrington and J. Dos Santos-Veiga, *Mol. Phys.* **5**, 21 (1962).

¹⁰⁶ R. L. Ward, *J. Am. Chem. Soc.* **84**, 332 (1962).

¹⁰⁷ C. A. McDowell, K. F. Paulus, and J. R. Rowlands, *Proc. Chem. Soc.* **60** (1962).

¹⁰⁸ A. Carrington, *Quart. Rev. (London)* **17**, 67 (1963).

¹⁰⁹ N. M. Atherton, F. Gerson, and J. N. Murrell, *Mol. Phys.* **5**, 509 (1962).

¹¹⁰ J. R. Bolton, A. Carrington, and J. Dos Santos-Veiga, *Mol. Phys.* **5**, 465 (1962).

¹¹¹ G. Fraenkel, R. E. Carter, A. McLachlan, and J. H. Richards, *J. Am. Chem. Soc.* **82**, 5846 (1960).

¹¹² T. Schaefer and W. G. Schneider, *Can. J. Chem.* **41**, 966 (1963).

¹¹³ W. Brügel, *Z. Elektrochem.* **66**, 159 (1962).

¹¹⁴ G. S. Reddy, R. T. Hobgood, Jr., and J. H. Goldstein, *J. Am. Chem. Soc.* **84**, 336 (1962).

^{114a} R. F. M. White, in "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Vol. II, p. 141 *et seq.* Academic Press, New York, 1963.

¹¹⁵ R. D. Brown and M. L. Heffernan, *Australian J. Chem.* **9**, 83 (1956).

¹¹⁶ C. A. Coulson, *Proc. Roy. Soc. (London)* **169A**, 413 (1939).

TABLE VII
 π -ELECTRON DENSITIES IN PYRIDINE¹¹²

Position	Pyridine, q				Pyridinium ion, q		
	Exptl. ^a	HMO ^b	SCF-CI ^c	VESCF ^d	Exptl. ^a	HMO ^b	VESCF ^d
2	—	0.923	0.951	0.952	0.854	0.759	0.899
3	1.014	1.005	1.010	1.004	0.915	1.012	0.927
4	0.976	0.950	0.979	0.981	0.862	0.835	0.829

^a Electron densities derived from proton chemical shifts.¹¹²

^b Taken from ref. 115.

^c Taken from ref. 58.

^d Taken from ref. 24, p. 554.

The three C—N bond length–bond order dependence curves proposed in the literature^{117–119} do not differ significantly; an extension of the amount of data on which they are based would seem desirable. The usual dependence can be used for the prediction of C—C bond lengths in nitrogen-containing heterocyclic compounds. Although the agreement between HMO bond orders and experimental bond lengths is satisfactory (cf. pyridine,^{118, 119} pyrazine,¹¹⁹ tetrazine,¹²³ pyrimidine,¹¹⁸ *sym.*-triazine,¹¹⁸ acridine,^{120, 121} dibenz[*a,j*]acridine,¹²² phenazine,¹¹⁸ and melamine¹¹⁸), we deem it desirable to reinvestigate the general applicability of the bond length–bond order dependence with respect to its splitting into partial dependences for individual types of bonds.¹²⁴

V. Chemical Reactivity

Attention has been paid to heterocyclic reactivity since the very beginning of applications of quantum chemistry to problems in organic chemistry.^{1, 2, 125, 126} Numerous papers^{127–137} reported HMO and VB calculations of π -electron densities and bond orders for models

¹¹⁷ E. G. Cox and G. A. Jeffrey, *Proc. Roy. Soc. (London)* **207A**, 110 (1951).

¹¹⁸ T. H. Goodwin and A. L. Porte, *J. Chem. Soc.* 3595 (1956).

¹¹⁹ T. Anno, M. Ito, R. Shimada, A. Sadô, and W. Mizushima, *Bull. Chem. Soc. Japan* **30**, 638 (1957).

¹²⁰ D. C. Phillips, *Acta Cryst.* **9**, 237 (1956).

¹²¹ D. C. Phillips, F. R. Ahmed, and W. H. Barnes, *Acta Cryst.* **13**, 365 (1960).

¹²² R. Mason, *Nature* **179**, 465 (1957).

¹²³ F. Bertinotti, G. Giacomello, and A. M. Liquori, *Acta Cryst.* **9**, 510 (1956).

¹²⁴ C. Vroelant and R. Daudel, *Compt. Rend.* **228**, 399 (1949).

¹²⁵ G. W. Wheland and L. Pauling, *J. Am. Chem. Soc.* **57**, 2086 (1935).

¹²⁶ G. W. Wheland, *J. Am. Chem. Soc.* **64**, 900 (1942).

¹²⁷ H. C. Longuet-Higgins and C. A. Coulson, *Trans. Faraday Soc.* **43**, 87 (1947).

¹²⁸ J. Ploquin, *Compt. Rend.* **226**, 245 (1948).

¹²⁹ P. Daudel, R. Daudel, N. P. Buu-Hoi, and M. Martin, *Bull. Soc. Chim. France* 1202 (1948).

¹³⁰ P. Yvan, *Compt. Rend.* **229**, 622 (1949).

¹³¹ C. A. Coulson and J. Jacobs, *J. Chem. Soc.* 1983 (1949).

¹³² C. Sandorfy and P. Yvan, *Compt. Rend.* **229**, 715 (1949).

¹³³ C. Sandorfy, *Bull. Soc. Chim. France* 615 (1949).

¹³⁴ C. Sandorfy and P. Yvan, *Bull. Soc. Chim. France* 131 (1950).

¹³⁵ I. Samuel, *Compt. Rend.* **231**, 1146 (1950).

¹³⁶ C. Sandorfy, C. Vroelant, P. Yvan, O. Chalvet, and R. Daudel, *Bull. Soc. Chim. France* 304 (1950).

¹³⁷ P. O. Löwdin, *J. Chem. Phys.* **19**, 1323 (1951).

of heterocyclic compounds (pyridine, quinoline, isoquinoline, and azaanthracenes), and it has been shown a number of times that the reactivity of these compounds can be rationalized in terms of the stated indices and/or localization energies. Similar conclusions were reached in a study of frontier electron densities.¹³⁸

A systematic and intensive theoretical study of reactivity has been reported by Brown and his colleagues,^{8, 115, 139-142} who discussed the reactivity of pyridine, quinoline, and isoquinoline in terms of localization energies. They investigated the values of these indices, first of all for electrophilic substitution, with regard to the value of the Coulomb integral of the heteroatom orbital and the orbitals adjacent to it (auxiliary inductive parameters). They demonstrated that the course of electrophilic substitution can be estimated from theoretical reactivity indices if π -electron densities are used for reactions that occur readily and localization energies for those occurring only reluctantly.

Interrelations between static and dynamic reactivity indices were investigated using models of pyridine and quinoline.¹³⁶

Dewar and Maitlis¹⁴³ discussed quite successfully the course of nitration in series of pyridine-like heterocycles in terms of the Dewar reactivity numbers. There is a continuing interest in the electronic structure of pyridine^{65, 144-146}; a model of this compound has been studied by the ASP MO LCAO SCF (antisymmetrized products) method in the π -electron approximation.¹⁴⁶ The semi-empirical parameters¹⁴⁶ were obtained from the most recent values of ionization potentials and electron affinities, and bicentric repulsion integrals were computed theoretically.

A detailed study of the reactivity of eleven pyridine-like heterocycles has been reported by Coppens and Nasielski.⁹ The authors used the simple MO method taking the value 0.5 for δ_N and allowing for an

¹³⁸ K. Fukui, T. Yonezawa, Ch. Nagata, and H. Shingu, *J. Chem. Phys.* **22**, 1433 (1954).

¹³⁹ R. D. Brown, *J. Chem. Soc.* 272 (1956).

¹⁴⁰ R. D. Brown and R. D. Harcourt, *J. Chem. Soc.* 3451 (1959).

¹⁴¹ R. D. Brown and R. D. Harcourt, *Tetrahedron* **8**, 23 (1960).

¹⁴² R. D. Brown, B. A. W. Collier, and R. D. Harcourt, *Australian J. Chem.* **14**, 643 (1961).

¹⁴³ M. J. S. Dewar and P. M. Maitlis, *J. Chem. Soc.* 2521 (1957).

¹⁴⁴ R. A. Barnes, *J. Am. Chem. Soc.* **81**, 1935 (1959).

¹⁴⁵ E. Vincent and J. Metzger, *Bull. Soc. Chim. France* 2039 (1962).

¹⁴⁶ R. L. Miller, P. G. Lykos, and H. N. Schmeising, *J. Am. Chem. Soc.* **84**, 4623 (1962).

inductive effect at all carbon orbitals of the conjugated skeleton. A comparison with experimental data was restricted to nucleophilic substitution (in the parent skeletons and derivatives) and basicity.

Most of the previous results have been briefly summarized by Streitwieser,³ who pointed out the special situation of positions adjacent to the heteroatom. A very thorough and critical review of a major portion of the studies just mentioned has been published by Ridd¹⁴⁷; it seems useful to refer the reader to his paper and then concentrate on some additional aspects of the theory of reactivity of pyridine-like heterocyclic compounds.

It should be stated at the beginning that despite quite numerous partial successes the present state of the quantum-chemical theory of reactivity is far from satisfactory. First of all, it is not clear whether the present shortcomings are due to the non-adequacy of models of activated complexes or to the drastic approximations made in the calculation of the energy of the activated complex and the reactants. On the other hand, some other deficiencies of most of the reported attempts to interpret reactivity in terms of the theory are obvious; the very nature of the HMO method is thought¹⁴⁸ to make it necessary to treat as large sets of theoretical and experimental data as possible and, in addition, to respect the distinction in properties of the three classes of positions mentioned (in this connection we do not refer to the difference in the stereochemistry of these positions).

A correct approach in the theoretical treatment of a kinetic problem would be to calculate, in a suitable approximation, the energies of adequate models of the activated complex and of the reactants and to compare the difference of these energies with the free energy of activation or with the logarithm of the rate constant of the reaction studied. However, such a procedure requires a separate treatment of every reaction series and a detailed knowledge of reaction mechanisms. It is the purpose of theoretical indices (which characterize usually only one of the reacting species) to give a true picture of the relative reactivity for a certain type of reaction, e.g. electrophilic substitution regardless of the detailed structure of the attacking agent. The advantages of such an approach are evident; it remains to be decided whether it is justified. This has been found to be the case with benzenoid hydrocarbons

¹⁴⁷ J. H. Ridd, in "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Vol. I, p. 109. Academic Press, New York, 1963.

¹⁴⁸ See article by R. Zahradník, in this volume.

since there exists a parallelism between the π -electron contribution to the activation energy for models of a substitution reaction and the usual indices.¹⁴⁹ No such investigation has been reported for the models of pyridine-like compounds; in view of the far-reaching similarity between the models of these two groups of substances it seems reasonable to anticipate the existence of a correlation of this kind.

The problem in question being rather complicated, we consider it suitable to divide the following considerations into three parts. In the first part the interrelations between various indices of chemical reactivity are examined since this can yield some information which might prove useful when trying to interpret experimental data in parts B and C of Section V.

A. INTERRELATIONS BETWEEN INDICES OF CHEMICAL REACTIVITY

It was found years ago¹³⁶ that atom localization energies are correlated with free valences and autopolarizabilities.

Recently, a series of models of 16 polynuclear pyridine-like heterocycles (Fig. 9 shows formulas of eleven of these) were treated using the HMO approximation⁷ ($\delta_N = 0.5$, inductive effect not allowed for) and the following reactivity indices calculated: π -electron densities (q), bond orders (p), free valences ($F, N_{max} = \sqrt{3}$), Wheland's atom localization energies (A_e, A_r, A_n), and superdelocalizabilities, both exact (S_e, S_r, S_n) and approximate (S'_e, S'_r, S'_n). Atom-atom polarizabilities¹⁵⁰ (π_{ij}) had been calculated earlier.¹⁵¹ Some of the indices calculated are presented in Section VI, B.

It has been demonstrated⁷ that the following pairs of indices are very closely correlated: $q-\pi_{ij}$, $F-A_r$, $F-S_r$ (hence also S_r-A_r), S_e-A_e , and S_n-A_n . The correlation between q and π_{ij} is very close (Fig. 10); these two indices do not exhibit any significant correlation with any of the others, however. The π -electron densities based on the present

¹⁴⁹ R. Zahradník and J. Koutecký, *Collection Czech. Chem. Commun.* **28**, 904 (1963).

¹⁵⁰ C. A. Coulson and H. C. Longuet-Higgins, *Proc. Roy. Soc. (London)* **191A**, 39 (1947).

¹⁵¹ C. A. Coulson and R. Daudel, "Dictionary of Values of Molecular Constants." Mathematical Inst., Oxford, and Centre de Chimie Theorique de France, Paris, 1955.

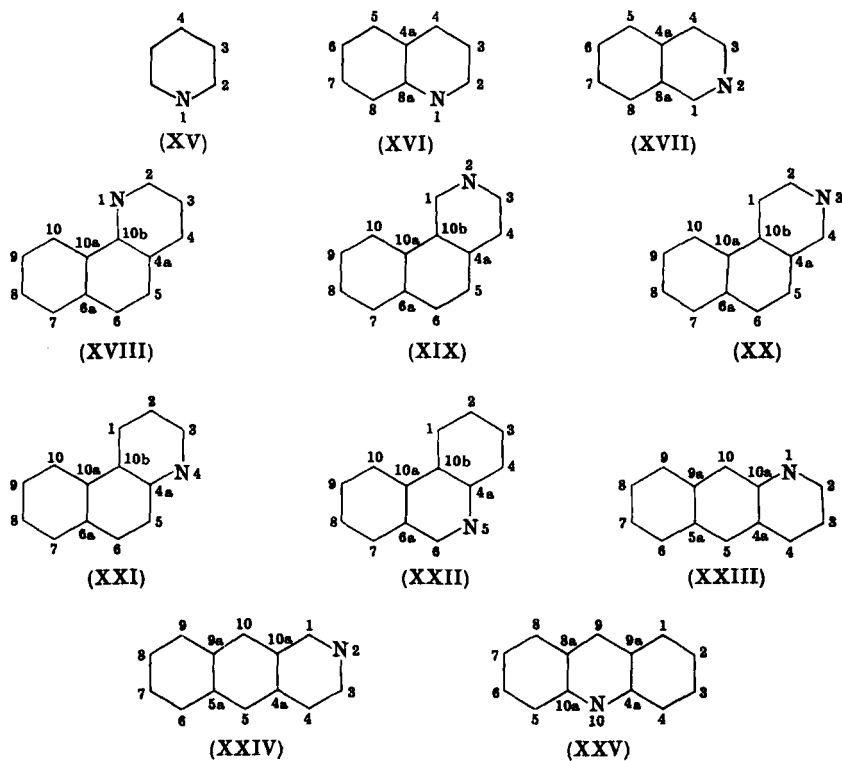
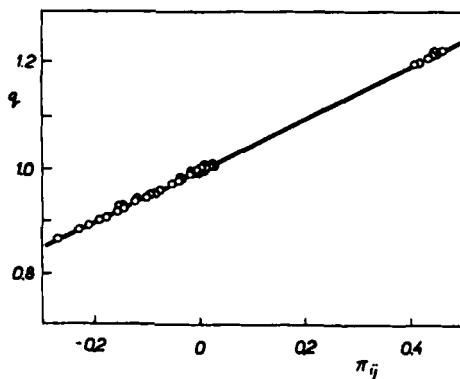


FIG. 9. Formulas of some polynuclear pyridine-like heterocycles.

FIG. 10. The plot of π -electron densities (q) against atom-atom polarizabilities (π_{ij}).⁷

model⁷ are found to be approximately linearly dependent on those obtained with models in which the inductive effect is allowed for.⁹ The plot shows a splitting according to classes of positions, the data for positions adjacent to heteroatoms being separated particularly strongly, which is quite comprehensible.

Worth mentioning is the finding that the radical reactivity indices (F , A_r , and S_r) are closely interrelated. Figure 11 shows the plot of F against S_r as an example; the plot is similar to those found for benzenoid hydrocarbons.²⁷ In addition to a significant separation of data for positions of class 0, 1, and 2, however, a separation of data for positions

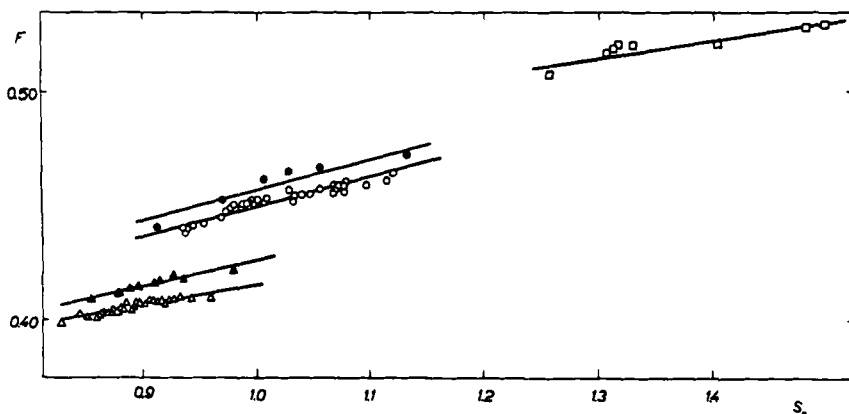


FIG. 11. Free valence (F) plotted against radical superdelocalizability (S_r).⁷ Designation (class of position²⁷): Δ (0), \circ (1), \square (2). Solid symbols indicate data for positions adjacent to the nitrogen atom.

adjacent to the heteroatom is apparent. In this connection it seems useful to recall the difficulties encountered in explaining the experimental reactivity of just these positions as well as their special nature as stated earlier.^{3,8}

The plots of S_e against A_e and of S_n against A_n resemble the above-mentioned correlation of F with S_r .⁷ Theoretically, the indices A and S thus appear roughly equivalent. On the other hand, it has been found that the approximate superdelocalizability fails to parallel any of the foregoing indices, as is also the case with benzenoid hydrocarbons.²⁷ It can also be stated that although Brown's Z factor¹⁵² appears very

¹⁵² R. D. Brown, *J. Chem. Soc.* 2232 (1959).

attractive in principle (it considers explicitly the nature of both the reagent and the substrate) we have not considered it in detail since in the form suggested it actually stands close to approximate super-delocalizability.

It has been further found⁷ that there is a correlation between the indices q , F , and S calculated for models of conjugated acids (such as the pyridinium cation, $\delta_{N^+} = 2$) with the same indices for a model in which $\delta_N = 0.5$.

Finally, satisfactory parallelism has been found⁷ between the indices q , p , and F calculated by Amos and Hall⁹⁷ using the SCF MO LCAO method for five models of pyridine-like compounds and the same indices derived from HMO calculations ($\delta_N = 0.5$).

B. COURSE OF SUBSTITUTION REACTIONS

It is well known that not all attempts to explain the reactivity of individual positions in electrophilic substitution reactions have been successful. There are three main lines along which attempts have been made to remove discrepancies between theory and experiment (for a summary, see ref. 147): (1) introduction into the HMO treatment of additional empirical parameters (inductive effect), (2) invoking the addition-elimination mechanism, and (3) invoking different reactivity of the protonated and unprotonated forms.

In ref. 7 are summarized the bases for our belief that it is useful at the present stage of development of the experimental and theoretical chemistry of pyridine-like compounds to examine the extent to which theory agrees with experiment under the simplest assumptions possible as far as both the theoretical treatment of the models and the explanation of substitution reaction mechanisms are concerned. The principal requirement is to choose a uniform treatment of all data on reactivity, at least at the outset, thus avoiding the introduction of more or less helpful auxiliary assumptions, which is often done to obtain agreement with experiment for a certain limited amount of data. Let us quote two cases as an illustration: Even though it is possible that some of the discrepancies found were due to different reactivities of the protonated and unprotonated forms, the finding that reactivity indices for models of these two forms are parallel (see Section V, A) prompts one to be careful in this regard. Recently, however, convincing evidence has been presented that the electrophilic, acid-catalyzed, hydrogen exchange of 2,6-lutidine and 2,4,6-collidine occurs by reactions of

these pyridines in their protonated forms.^{152a} Protonated forms are also involved in the nitration of collidine,^{152b} quinoline,^{152c,d} and isoquinoline.^{152e} On the contrary, the splitting of theoretical data into classes and subclasses has not yet been used much (for benzenoid hydrocarbons, examples of such behavior have also been found in correlations of experimental rate constants with theoretical data). In this connection there is a disturbing lack of suitable experimental data; the field has witnessed no experimental studies like those made with benzenoid hydrocarbons (see, e.g., refs. 153 and 154).

In terms of HMO reactivity indices ($\delta_N = 0.5$) the available data on the course of substitution reactions¹⁵⁵⁻¹⁵⁹ (see also refs. 7 and 147), mostly on electrophilic substitution, yield the following picture: With compounds XV-XVII^{159a} the theoretical reactivity order is in satisfactory agreement with experimental findings provided that Brown's idea mentioned above on the distinction between readily and reluctantly occurring reactions is accepted; there is no need to emphasize that this valuable idea requires further scrutiny, however. On the other hand, with compounds XVIII, XXI, and XXII the position of maximum reactivity does not agree with any of the indices mentioned. The reason for this has not been found.⁷ With compound XXV the yields of the nitro derivatives indicate that the reactivity order is $2 > 4 > 1$; S_e values are in the order $4 > 1 > 2$. It is worth noting that position 2 is of class 0.

In the case of nucleophilic reactions, the positions of minimum π -

^{152a} A. R. Katritzky and B. J. Ridgewell, *J. Chem. Soc.* 3743 (1963).

^{152b} A. R. Katritzky and B. J. Ridgewell, *J. Chem. Soc.* 3882 (1963).

^{152c} R. B. Moodie, K. Schofield, and M. J. Williamson, *Chem. Ind. (London)* 1283 (1963).

^{152d} M. W. Austin and J. H. Ridd, *J. Chem. Soc.* 4204 (1963).

¹⁵³ M. J. S. Dewar, T. Mole, and E. W. T. Warford, *J. Chem. Soc.* 3581 (1956).

¹⁵⁴ G. Dallinga, A. A. V. Stuart, P. J. Smit, and E. L. Mackor, *Z. Elektrochem.* 61, 1019 (1957).

¹⁵⁵ H. S. Mosher, in "Heterocyclic Compounds" (R. C. Elderfield, ed.) Vol. I. Wiley, New York, 1950.

¹⁵⁶ A. Albert, "Heterocyclic Chemistry." Athlone Press, London, 1959.

¹⁵⁷ E. Klingsberg, "Pyridine and Its Derivatives, Parts I-III." Interscience, New York, 1960, 1961, and 1962 respectively.

¹⁵⁸ A. R. Katritzky and J. M. Lagowski, "Heterocyclic Chemistry." Methuen, London, 1960.

¹⁵⁹ G. M. Badger, "The Chemistry of Heterocyclic Compounds." Academic Press, New York, 1960.

^{159a} See Table X for identification of compounds XV-XXV.

electron density are those of maximum reactivity (with the single exception of cyanation of compound XVIII⁷). The agreement between A_n or S_n values and experimental data is less satisfactory.

As for radical substitutions in compounds XV, XVII, XXV, and some other compounds, the F values (hence also A_r and S_r values, cf. section V, A) correctly predict the experimental reactivity order. The calculated and experimental orders disagree in the case of compounds XXI and, particularly, XVI; the latter case (radical phenylation of quinoline) represents a serious failure of the theory, for the experimental study was very thorough.¹⁶⁰ It is worth noting that in the compounds which have no meso-position the center of radical reactivity is the position adjacent to the nitrogen atom (with the exception of the just mentioned phenylation of quinoline).

C. INTERPRETATION OF EQUILIBRIUM DATA

For pyridine, quinoline, isoquinoline, and acridine, the differences in the π -electronic energies of the protonated form and the free base have been calculated at several levels of sophistication, from the HMO method to the CI SCF method.¹⁶¹ The ΔW values obtained are linearly interrelated, which supports the view that the HMO data are meaningful. In this connection, considerable attention has been paid to the role of solvation energies in acido-basic equilibria.¹⁶¹

The pK values have been determined for several pyridine-like heterocycles.^{162, 162a, 162b} Their relation to the difference (ΔW) in π -electronic energies of models of the conjugated acids (W_{N^+}) and of the free bases (W_N) has been investigated.⁷ Values for W_{N^+} , W_N , ΔW , π -electron densities at the nitrogen atom in the free base (q), and localization energies (A_j) of the position in the parent hydrocarbon in which there is a nitrogen atom in the heterocycle are given in Table VIII.

The number of experimental pK values is insufficient for a quantitative study of the relationship to theoretical quantities, especially in

¹⁶⁰ K. H. Pausacker, *Australian J. Chem.* **11**, 200 (1958).

¹⁶¹ R. Daudel, *Tetrahedron* **19**, Suppl. 2, 351 (1963) (gives references to previous work).

¹⁶² A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.* 2240 (1948).

¹⁶² (a) H. C. Brown, D. H. McDaniel, and O. Häfliger, in "Determination of Organic Structures by Physical Methods" (E. A. Braude and F. C. Nachod, eds.), Academic Press, New York, 1955; (b) A. Albert, in "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Chapter 1, Vol. I. Academic Press, New York, 1963.

TABLE VIII
BASICITY OF MONOAZINES⁷

Compound	q^a	$W_{N^+}^b$	W_N^c	$\Delta W = W_{N^+} - W_N$	A^d	pK(exptl.) _I ^e	pK(exptl.) _{II} ^f
Pyridine	1.195	10.698	8.549	2.149	2.536	5.14	—
Quinoline	1.216	16.440	14.238	2.202	2.299	4.85	—
Isoquinoline	1.198	16.391	14.233	2.158	2.479	5.14	—
Benzo[<i>h</i>]quinoline	1.210	22.189	20.002	2.187	2.367	4.25	3.15
Benz[<i>h</i>]isoquinoline	1.200	22.162	20.000	2.162	2.454	—	—
Benz[<i>f</i>]isoquinoline	1.197	22.154	19.999	2.155	2.499	—	4.56 ^g
Benzo[<i>f</i>]quinoline	1.214	22.200	20.003	2.197	2.320	5.15	3.90
Phenanthridine	1.216	22.206	20.004	2.202	2.299	—	3.30
Benzo[<i>g</i>]quinoline	1.221	22.085	19.870	2.215	2.230	5.05	3.84
Benz[<i>g</i>]isoquinoline	1.201	22.030	19.864	2.166	2.423	—	—
Acridine	1.254	22.164	19.878	2.286	2.013	5.60	—
Benz[<i>a</i>]acridine	1.248	27.939	25.664	2.275	2.050	4.70	4.16
Benz[<i>c</i>]acridine	1.240	27.920	25.662	2.258	2.102	—	3.45
Naphtho[2,3- <i>g</i>]quinoline	1.223	27.706	25.487	2.219	2.200	—	—
Naphth[2,3- <i>g</i>]isoquinoline	1.203	27.651	25.482	2.169	2.384	—	—
Benz[<i>b</i>]acridine	1.267	27.810	25.499	2.311	1.932	—	4.52

^a π -Electron density at the heteroatom, $\delta_N = 0.5$.

^b π -Electronic energy of the model of conjugated acid, $\delta_{N^+} = 2.0$.

^c π -Electronic energy of the model of free base, $\delta_N = 0.5$.

^d Atom localization energy for the parent hydrocarbon in the position in which the heterocycle carries a nitrogen atom.

^e Water, according to refs. 162 and 162a.

^f Aqueous ethanol (50%), according to refs. 162 and 162a.

^g Aqueous methanol, according to ref. 173.

view of the splitting in the plot of pK against ΔW into three regions according to the class of the position in which the nitrogen atom is bound. Therefore the relation can only be evaluated qualitatively. It is clear that a larger decrease in π -electronic energy when going from a base to its conjugate acid means a higher pK provided that the nitrogen atom is in a position of the same class in all compounds compared. It is worth noting that there is a close correlation between W and q as well as between W and A , the classes being somewhat distinguished in these cases too. Thus it can be understood that, for positions of the same class there is correlation, or at least parallelism, between pH values and q or A .

The interrelation of pK values and q can also be demonstrated theoretically. This has been done by Longuet-Higgins¹⁶³ who proved that there is a correlation between pK values and q within extensive groups of derivatives (amino, hydroxy) of pyridine-like heterocycles.^{163a} Also, he demonstrated that aminoaza heterocyclic compounds are protonated exclusively at the heterocyclic nitrogen atom. In the correlation he used π -electron densities based on his well-known method¹⁶⁴ which makes use of special properties of non-bonding orbitals in models of odd alternant hydrocarbons.

VI. Appendix

The appendix summarizes results of HMO calculations for models of pyridine-like heterocycles. The data presented in Tables IX–XII refer to $\delta_N = 0.5$.

A. ENERGY CHARACTERISTICS

The following quantities are presented in Table IX: total π -electronic energy (W), its deviation from that of the parent hydrocarbon (ΔW), energies of the four frontier π -molecular orbitals (k_2 , k_1 , k_{-1} , and k_{-2} ; k_1 is the highest occupied orbital, HOMO; k_{-1} is the lowest free orbital, LFMO), $N \rightarrow V_1$ transition energy [$E(N \rightarrow V_1)$] and the atom localization energy for the parent hydrocarbon in the position in which the heterocycle has a nitrogen atom.

¹⁶³ H. C. Longuet-Higgins, *J. Chem. Phys.* **18**, 275 (1950).

^{163a} J. Ploquin, *J. Chim. Phys.* **47**, 198 (1950).

¹⁶⁴ H. C. Longuet-Higgins, *J. Chem. Phys.* **18**, 265 (1950).

TABLE IX
ENERGY CHARACTERISTICS FOR HETEROANALOGUES OF BENZENOID HYDROCARBONS (β -UNITS)^a

No. ^a	Parent compound	Position ^b	W	ΔW	k_2	k_1	k_{-1}	k_{-2}	$E(N \rightarrow V_1)$	A_i
I	Benzene	1	8.549	0.549	1.167	1.000	-0.841	-1.000	1.841	2.536
II	Naphthalene	1	14.238	0.555	1.000	0.703	-0.527	-1.000	1.230	2.299
		2	14.233	0.550	1.078	0.646	-0.576	-0.920	1.222	2.479
III	Phenanthrene	1	20.003	0.554	0.813	0.648	-0.536	-0.741	1.184	2.320
		2	19.999	0.550	0.834	0.606	-0.603	-0.687	1.209	2.499
		3	20.000	0.551	0.769	0.648	-0.550	-0.769	1.199	2.454
		4	20.002	0.553	0.835	0.623	-0.563	-0.711	1.187	2.367
		9	20.004	0.555	0.778	0.683	-0.518	-0.766	1.201	2.299
IV	Anthracene	1	19.870	0.556	1.000	0.459	-0.364	-0.921	0.823	2.230
		2	19.864	0.551	1.000	0.436	-0.388	-0.912	0.823	2.423
		9	19.878	0.565	1.000	0.514	-0.325	-1.000	0.840	2.013
V	Triphenylene	1	25.827	0.553	0.723	0.684	-0.613	-0.684	1.297	2.374
		2	25.825	0.550	0.729	0.684	-0.620	-0.684	1.304	2.476
VI	Benzo[c]phenanthrene	1	25.741	0.554	0.669	0.611	-0.507	-0.659	1.118	2.332
		2	25.738	0.551	0.699	0.577	-0.543	-0.627	1.120	2.461
		3	25.737	0.550	0.666	0.589	-0.535	-0.658	1.124	2.477
		4	25.742	0.555	0.691	0.598	-0.510	-0.646	1.107	2.312
		5	25.742	0.555	0.716	0.598	-0.502	-0.639	1.100	2.297
		6	25.742	0.555	0.748	0.571	-0.541	-0.592	1.112	2.323
VII	Pyrene	1	23.063	0.557	0.896	0.510	-0.377	-0.862	0.887	2.189
		2	23.054	0.549	0.954	0.445	-0.445	-0.779	0.890	2.549
		4	23.060	0.555	0.885	0.484	-0.298	-0.860	0.782	2.275

TABLE IX—continued

No. ^a	Parent compound	Position ^b	<i>W</i>	ΔW	<i>k</i> ₂	<i>k</i> ₁	<i>k</i> ₋₁	<i>k</i> ₋₂	<i>E</i> (<i>N</i> → <i>V</i> ₁)	<i>A</i> ₁
VIII	Chrysene	1	25.745	0.555	0.795	0.556	−0.470	−0.782	1.026	2.303
		2	25.740	0.550	0.832	0.526	−0.510	−0.725	1.036	2.492
		3	25.741	0.551	0.803	0.543	−0.488	−0.770	1.031	2.448
		4	25.743	0.553	0.803	0.543	−0.484	−0.757	1.027	2.349
		5	25.743	0.553	0.817	0.542	−0.485	−0.738	1.027	2.348
		6	25.746	0.556	0.793	0.590	−0.445	−0.792	1.035	2.248
IX	Benz[<i>a</i>]anthracene	1	25.654	0.553	0.799	0.452	−0.452	−0.617	0.905	2.370
		2	25.652	0.551	0.733	0.470	−0.428	−0.690	0.898	2.436
		3	25.651	0.550	0.747	0.456	−0.446	−0.665	0.902	2.488
		4	25.656	0.554	0.794	0.462	−0.435	−0.633	0.897	2.316
		5	25.657	0.555	0.763	0.487	−0.405	−0.675	0.892	2.258
		6	25.657	0.555	0.739	0.490	−0.403	−0.690	0.894	2.260
		7	25.664	0.563	0.715	0.553	−0.360	−0.715	0.913	2.050
		8	25.657	0.556	0.721	0.500	−0.397	−0.709	0.897	2.246
		9	25.652	0.551	0.740	0.468	−0.430	−0.684	0.898	2.446
		10	25.652	0.551	0.716	0.477	−0.421	−0.713	0.898	2.430
		11	25.657	0.555	0.733	0.492	−0.403	−0.696	0.895	2.258
		12	25.662	0.561	0.744	0.523	−0.375	−0.697	0.898	2.102
X	Naphthacene	1	25.487	0.557	0.835	0.321	−0.265	−0.714	0.586	2.200
		2	25.482	0.551	0.792	0.311	−0.277	−0.750	0.588	2.384
		5	25.499	0.568	0.803	0.370	−0.227	−0.756	0.598	1.932
XI	Perylene	1	28.802	0.557	1.000	0.387	−0.305	−0.908	0.691	2.203
		2	28.795	0.550	1.000	0.353	−0.340	−0.870	0.693	2.510
		3	28.804	0.559	1.000	0.399	−0.294	−0.929	0.693	2.139

XII	Benzo[a]pyrene	1	28.780	0.558	0.803	0.427	−0.314	−0.800	0.741	2.152
		2	28.771	0.549	0.826	0.372	−0.369	−0.749	0.742	2.542
		3	28.780	0.558	0.839	0.419	−0.319	−0.765	0.738	2.168
		4	28.777	0.556	0.809	0.406	−0.331	−0.787	0.737	2.242
		5	28.777	0.555	0.803	0.406	−0.331	−0.798	0.737	2.240
		6	28.789	0.567	0.806	0.469	−0.286	−0.799	0.755	1.962
		7	28.778	0.556	0.831	0.404	−0.333	−0.759	0.736	2.232
		8	28.772	0.550	0.862	0.375	−0.367	−0.721	0.741	2.488
		9	28.773	0.551	0.802	0.397	−0.342	−0.801	0.739	2.380
		10	28.775	0.553	0.849	0.384	−0.353	−0.728	0.738	2.336
		11	28.775	0.553	0.832	0.385	−0.352	−0.742	0.738	2.342
		12	28.778	0.556	0.802	0.412	−0.327	−0.801	0.738	2.220
XIII	Dibenz[a,h]anthracene	1	31.433	0.553	0.714	0.475	−0.471	−0.613	0.946	2.364
		2	31.431	0.551	0.685	0.493	−0.446	−0.683	0.939	2.438
		3	31.430	0.550	0.717	0.474	−0.472	−0.633	0.946	2.489
		4	31.435	0.555	0.702	0.488	−0.448	−0.643	0.936	2.309
		5	31.436	0.556	0.695	0.517	−0.418	−0.673	0.935	2.259
		6	31.435	0.555	0.684	0.509	−0.426	−0.684	0.935	2.277
		7	31.440	0.560	0.714	0.530	−0.401	−0.663	0.931	2.130
XIV	Dibenz[a,j]anthracene	1	31.432	0.553	0.652	0.492	−0.492	−0.561	0.983	2.363
		2	31.430	0.551	0.634	0.507	−0.466	−0.601	0.974	2.443
		3	31.429	0.550	0.632	0.496	−0.484	−0.596	0.980	2.485
		4	31.433	0.554	0.655	0.499	−0.473	−0.571	0.972	2.315
		5	31.434	0.555	0.669	0.515	−0.445	−0.584	0.960	2.268
		6	31.435	0.556	0.639	0.529	−0.437	−0.605	0.966	2.270
		7	31.441	0.562	0.618	0.595	−0.395	−0.618	0.990	2.082
		14	31.438	0.559	0.618	0.549	−0.423	−0.618	0.972	2.176

^a See Fig. 3.

^b Position in which a nitrogen atom has been substituted for a carbon atom.

TABLE X
QUANTUM-CHEMICAL REACTIVITY INDICES OF HETEROANALOGUES OF AROMATIC HYDROCARBONS⁷

No. ^a	Compound	Position ^a	Class ^b	q	π_{ij}	F	S_e	S_r	S_a
XV	Pyridine	1	N	1.1952	0.398	—	0.8167	0.8167	0.8167
		2	O(N)	0.9230	—0.157	0.4090	0.7285	0.8535	0.9785
		3	O	1.0045	0.009	0.3978	0.8324	0.8324	0.8324
		4	O	0.9499	—0.102	0.4023	0.7240	0.8490	0.9740
XVI	Quinoline	1	N	1.2161	0.443	—	0.9689	0.9689	0.9689
		2	O(N)	0.8962	—0.213	0.4175	0.6922	0.9144	1.1366
		3	O	1.0085	0.018	0.4028	0.8705	0.8705	0.8705
		4	1	0.9319	—0.139	0.4574	0.8052	1.0274	1.2497
		5	1	0.9885	—0.023	0.4532	0.9451	1.0006	1.0562
		6	O	1.0031	0.007	0.4039	0.8719	0.8719	0.8719
		7	O	0.9842	—0.033	0.4053	0.8253	0.8808	0.9364
		8	1	1.0129	0.027	0.4506	0.9903	0.9903	0.9903
XVII	Isoquinoline	1	1(N)	0.8955	—	0.4648	0.8048	1.0270	1.2492
		2	N	1.1984	—	—	0.8549	0.8549	0.8549
		3	O(N)	0.9466	—	0.4135	0.8310	0.8866	0.9421
		4	1	1.0086	—	0.4514	0.9923	0.9923	0.9923
		5	1	1.0031	—	0.4525	0.9935	0.9935	0.9935
		6	O	0.9839	—	0.4052	0.8236	0.8791	0.9347
		7	O	1.0001	—	0.4044	0.8730	0.8730	0.8730
		8	1	0.9841	—	0.4537	0.9448	1.0004	1.0559
XVIII	Benzo[<i>h</i>]quinoline (4-azaphenanthrene)	1	N	1.2098	0.4292	—	0.9168	0.9168	0.9168
		2	O(N)	0.9077	—0.1893	0.4196	0.7447	0.9247	1.1047
		3	O	1.0073	0.0152	0.4009	0.8584	0.8584	0.8584

	4	1	0.9408	—0.1208	0.4340	0.8218	1.0018	1.1818
	5	1	0.9960	—0.0080	0.4515	0.9792	0.9992	1.0192
	6	1	1.0021	0.0042	0.4511	0.9967	0.9967	0.9967
	7	1	1.0000	0.0001	0.4501	0.9770	0.9770	0.9770
	8	0	0.9942	—0.0118	0.4027	0.8428	0.8428	0.8428
	9	0	1.0010	0.0021	0.4075	0.8926	0.8926	0.8926
	10	1	0.9917	—0.0170	0.4412	0.9224	0.9124	0.9024
XIX Benz[<i>h</i>]isoquinoline (3-azaphenanthrene)	1	1(N)	0.9075	—0.1893	0.4520	0.7886	0.9686	1.1486
	2	N	1.2002	0.4086	0.4354	0.8741	0.8741	0.8741
	3	0(N)	0.9398	—0.1235	0.4119	0.7972	0.8772	0.9572
	4	1	1.0086	0.0177	0.4486	0.9748	0.9748	0.9747
	5	1	1.0039	0.0080	0.4510	0.9962	0.9962	0.9962
	6	1	0.9792	—0.0423	0.4524	0.9259	1.0059	1.0859
	7	1	0.9959	—0.0083	0.4501	0.9587	0.9787	0.9987
	8	0	1.0001	0.0002	0.4024	0.8603	0.8603	0.8603
	9	0	0.9955	—0.0091	0.4079	0.8748	0.8949	0.9149
	10	1	1.0010	0.0021	0.4404	0.9388	0.9388	0.9388
XX Benz[<i>f</i>]isoquinoline (2-azaphenanthrene)	1	1	1.0074	0.0152	0.4392	0.9374	0.9374	0.9374
	2	0(N)	0.9397	—0.1235	0.4171	0.8287	0.9087	0.9887
	3	N	1.1974	0.4028	0.4293	0.8427	0.8427	0.8427
	4	1(N)	0.9053	—0.1935	0.4616	0.8247	1.0048	1.1848
	5	1	0.9928	—0.0146	0.4519	0.9799	0.9999	1.0198
	6	1	1.0001	0.0002	0.4514	0.9973	0.9973	0.9973
	7	1	1.0003	0.0006	0.4500	0.9769	0.9769	0.9769
	8	0	0.9947	—0.0107	0.4026	0.8423	0.8623	0.8823
	9	0	1.0001	0.0002	0.4076	0.8929	0.8929	0.8929
	10	1	0.9942	—0.0118	0.4407	0.9212	0.9412	0.9612

TABLE X—*continued*

No. ^a	Compound	Position ^a	Class ^b	q	π_{ij}	F	S_e	S_r	S_n
XXI	Benzo[<i>f</i>]quinoline (1-azaphenanthrene)	1	1	0.9409	−0.1208	0.4448	0.7861	0.9661	1.1461
		2	0	1.0085	0.0177	0.4062	0.8905	0.8905	0.8905
		3	0(N)	0.9059	−0.1935	0.4150	0.7153	0.8953	1.0753
		4	N	1.2143	0.4391	0.4808	0.9525	0.9524	0.9524
		5	1	1.0116	0.0242	0.4494	0.9938	0.9938	0.9938
		6	1	0.9780	−0.0450	0.4526	0.9280	1.0079	1.0879
		7	1	0.9952	−0.0098	0.4502	0.9594	0.9793	0.9993
		8	0	1.0003	0.0006	0.4023	0.8602	0.8602	0.8602
		9	0	0.9959	−0.0083	0.4077	0.8750	0.8951	0.9151
		10	1	1.0000	0.0001	0.4404	0.9391	0.9391	0.9391
XXII	Phenanthridine (9-azaphenanthrene)	1	1	1.0020	0.0042	0.4402	0.9384	0.9384	0.9384
		2	0	0.9793	−0.0423	0.4087	0.8237	0.9037	0.9837
		3	0	1.0001	0.0002	0.4024	0.8603	0.8603	0.8602
		4	1	0.9780	−0.0450	0.4513	0.9081	0.9881	1.0681
		5	1(N)	0.8686	−0.2700	0.4662	0.7329	1.0529	1.3729
		6	N	1.2159	0.4424	—	0.9718	0.9718	0.9718
		7	1	1.0116	0.0242	0.4480	0.9733	0.9733	0.9733
		8	0	0.9929	−0.0146	0.4030	0.8437	0.8637	0.8837
		9	0	1.0038	0.0080	0.4072	0.8915	0.8915	0.8915
		10	1	0.9960	−0.0080	0.4407	0.9213	0.9413	0.9613
XXIII	Benzo[<i>g</i>]quinoline (1-azaanthracene)	1	N	1.2213	0.4539	—	1.0440	1.0440	1.0439
		2	0(N)	0.8881	−0.2307	0.4224	0.6953	0.9765	1.2576
		3	0	1.0106	0.0220	0.4070	0.9180	0.9180	0.9180

XXIV Benz[<i>g</i>]isoquinoline (2-azaanthracene)	4	1	0.9262	—0.1513	0.4641	0.8366	1.1179	1.3992
	5	2	0.9802	—0.0402	0.5205	1.2023	1.3273	1.4523
	6	1	0.9958	—0.0084	0.4594	1.0451	1.0763	1.1075
	7	0	1.0019	0.0040	0.4086	0.9208	0.9208	0.9208
	8	0	0.9948	—0.0106	0.4090	0.8941	0.9254	0.9566
	9	1	1.0039	0.0080	0.4590	0.1713	1.0714	1.0714
	10	2	1.0205	0.0428	0.5169	1.3049	1.3049	1.3049
	1	1(N)	0.8871	—0.2307	0.4716	0.8335	1.1148	1.3961
	2	N	1.2012	0.4108	—	0.9021	0.9021	0.9021
	3	0(N)	0.9519	—0.0989	0.4178	0.9029	0.9342	0.9654
XXV Acridine (9-azaanthracene)	4	1	1.0107	0.0220	0.4577	1.0702	1.0702	1.0702
	5	2	1.0069	0.0142	0.5192	1.3107	1.3107	1.3107
	6	1	1.0019	0.0040	0.4592	1.0725	1.0725	1.0725
	7	0	0.9939	—0.0124	0.4090	0.8935	0.9247	0.9560
	8	0	1.0005	0.0010	0.4088	0.9215	0.9215	0.9216
	9	1	0.9947	—0.0106	0.4595	1.0446	1.0759	1.1071
	10	2	0.9732	—0.0544	0.5210	1.2007	1.3257	1.4508
	1	1	0.9805	0.0428	0.4600	0.9690	1.0941	1.2191
	2	0	1.0066	—0.0544	0.4079	0.9176	0.9176	0.9176
	3	0	0.9738	0.0142	0.4105	0.8217	0.9467	1.0717
	4	1	1.0201	—0.0402	0.4560	1.0624	1.0624	1.0625
	9	2	0.8954	0.5257	0.5265	0.9128	1.4128	1.9128
	10	N	1.2536	—0.2175	—	1.2606	1.2606	1.2606

^a See Fig. 9; for data on benz[*a*]acridine, benz[*c*]acridine, naphtho[2,3-*g*]quinoline, naphth[2,3-*g*]isoquinoline, benz[*b*]acridine, dibenz[*b,h*]acridine, see ref. 7.

^b See Section III and ref. 27; N indicates a nitrogen atom, *i*(N) is a position of class *i* adjacent to the nitrogen atom.

B. INDICES OF CHEMICAL REACTIVITY

Table X presents the following data for models of molecules XV–XXV: π -electron densities (q), atom–atom polarizabilities (π_{ij}), free valences (F , $N_{\max} = \sqrt{3}$), and exact superdelocalizabilities (S_e , S_r , and S_n). Table XI gives Wheland's atom-localization energies for a few molecules. Bond orders for molecules XV–XXV are compiled in Table XII.

TABLE XI
ATOM-LOCALIZATION ENERGIES OF VARIOUS HETEROCYCLIC COMPOUNDS
(β -UNITS)⁷

Compound No. ^a	Position ^a	Class ^b	A_e	A_r	A_n
XV	1	N	—	—	—
	2	O(N)	2.6718	2.5124	2.3529
	3	O	2.5381	2.5381	2.5381
	4	O	2.7011	2.5374	2.3737
XVI	1	N	—	—	—
	2	O(N)	2.7084	2.4698	2.2311
	3	O	2.4843	2.4843	2.4843
	4	1	2.4832	2.3050	2.1268
	5	1	2.3416	2.2968	2.2520
	6	O	2.4814	2.4814	2.4814
	7	O	2.5365	2.4754	2.4142
	8	1	2.3044	2.3044	2.3044
XVII	1	1(N)	2.4522	2.2781	2.1040
	2	N	—	—	—
	3	O(N)	2.5097	2.4494	2.3891
	4	1	2.3021	2.3021	2.3021
	5	1	2.2998	2.2998	2.2998
	6	O	2.5387	2.4771	2.4155
	7	O	2.4797	2.4797	2.4797
	8	1	2.3403	2.2954	2.2505
XX	1	1	2.3727	2.3727	2.3727
	2	O(N)	2.5075	2.4275	2.3475
	3	N	3.0512	3.0512	3.0512
	4	1(N)	2.4404	2.2934	2.1464
	5	1	2.3157	2.2998	2.2837

TABLE XI—*continued*

Compound No. ^a	Position ^a	Class ^b	A _e	A _r	A _n
XX	6	1	2.3022	2.3022	2.3022
	7	1	2.3219	2.3219	2.3219
	8	0	2.5233	2.4997	2.4761
	9	0	2.4574	2.4574	2.4574
	10	1	2.3866	2.3675	2.3484
XXI	1	1	2.5373	2.3683	2.1993
	2	0	2.4575	2.4575	2.4575
	3	0(N)	2.6698	2.4705	2.2712
	4	N	2.8716	2.8716	2.8716
	5	1	2.3030	2.3030	2.3030
	6	1	2.3564	2.2933	2.2302
	7	1	2.3327	2.3156	2.2985
	8	0	2.4971	2.4971	2.4971
	9	0	2.4722	2.4515	2.4308
	10	1	2.3651	2.3651	2.3651
XXIII	1	N	—	—	—
	2	0(N)	2.6539	2.4148	2.1757
	3	0	2.4285	2.4285	2.4284
	4	1	2.4044	2.2355	2.0665
	5	2	2.0617	2.0125	1.9633
	6	1	2.2486	2.2295	2.2105
	7	0	2.4240	2.4240	2.4240
	8	0	2.4485	2.4211	2.3937
	9	1	2.2324	2.2324	2.2323
	10	2	2.0203	2.0203	2.0203
XXIV	1	1(N)	2.3723	2.2075	2.0427
	2	N	—	—	—
	3	0(N)	2.4202	2.3931	2.3660
	4	1	2.2346	2.2346	2.2346
	5	2	2.0152	2.0152	2.0152
	6	1	2.2313	2.2313	2.2313
	7	0	2.4488	2.4213	2.3938
	8	0	2.4229	2.4229	2.4229
	9	1	2.2486	2.2295	2.2104
	10	2	2.0598	2.0105	1.9612

^a See Fig. 9.^b See Section III, ref. 27, and footnote b to Table X.

TABLE XII
BOND ORDERS FOR VARIOUS HETEROCYCLIC COMPOUNDS (p_{ij})^{a,7}

Bond ($i-j$)	p_{ij}	Bond ($i-j$)	p_{ij}	Bond ($i-j$)	p_{ij}
Pyridine (XV)					
1-2	0.6537	2-3	0.6694	3-4	0.6649
Quinoline (XVI)					
1-2	0.7065	2-3	0.6081	3-4	0.7212
4-4a	0.5535	4a-5	0.5549	5-6	0.7240
6-7	0.6042	7-8	0.7226	8-8a	0.5589
1-8a	0.5414	4a-8a	0.5197	—	—
Isoquinoline (XVII)					
1-2	0.7099	2-3	0.5906	3-4	0.7280
4-4a	0.5527	4a-5	0.5559	5-6	0.7237
6-7	0.6032	7-8	0.7245	8-8a	0.5539
1-8a	0.5574	4a-8a	0.5170	—	—
Benzo[h]quinoline (XVIII)					
1-2	0.6854	2-3	0.6270	3-4	0.7041
4-4a	0.5939	4a-5	0.5060	5-6	0.7745
6-6a	0.5064	6a-7	0.5751	7-8	0.7068
8-9	0.6225	9-10	0.7020	10-10a	0.5888
10a-10b	0.4638	1-10b	0.5766	4a-10b	0.5440
6a-10a	0.5415	—	—	—	—
Benz[h]isoquinoline (XIX)					
1-2	0.6869	2-3	0.6097	3-4	0.7104
4-4a	0.5730	4a-5	0.5074	5-6	0.7736
6-6a	0.5060	6a-7	0.5751	7-8	0.7068
8-9	0.6228	9-10	0.7013	10-10a	0.5903
10a-10b	0.4599	1-10b	0.5931	4a-10b	0.5407
6a-10a	0.5422	—	—	—	—
Benz[f]isoquinoline (XX)					
1-2	0.7048	2-3	0.6101	3-4	0.6926
4-4a	0.5778	4a-5	0.5053	5-6	0.7748
6-6a	0.5058	6a-7	0.5753	7-8	0.7067
8-9	0.6227	9-10	0.7017	10-10a	0.5896
10a-10b	0.4615	1-10b	0.5880	4a-10b	0.5410
6a-10a	0.5419	—	—	—	—

TABLE XII—*continued*

Bond (<i>i-j</i>)	p_{ij}	Bond (<i>i-j</i>)	p_{ij}	Bond (<i>i-j</i>)	p_{ij}
Benzo[<i>f</i>]quinoline (XXI)					
1-2	0.6983	2-3	0.6275	3-4	0.6895
4-4a	0.5617	4a-5	0.5100	5-6	0.7726
6-6a	0.5068	6a-7	0.5748	7-8	0.7070
8-9	0.6227	9-10	0.7016	10-10a	0.5900
10a-10b	0.4606	1-10b	0.5889	4a-10b	0.5437
6a-10a	0.5420	—	—	—	—
Phenanthridine (XXII)					
1-2	0.7012	2-3	0.6236	3-4	0.7054
4-4a	0.5786	4a-5	0.4938	5-6	0.7554
6-6a	0.5104	6a-7	0.5737	7-8	0.7070
8-9	0.6226	9-10	0.7007	10-10a	0.5911
10a-10b	0.4592	1-10b	0.5901	4a-10b	0.5442
6a-10a	0.5404	—	—	—	—
Benzo[<i>g</i>]quinoline (XXIII)					
1-2	0.7178	2-3	0.5919	3-4	0.7332
4-4a	0.5348	4a-5	0.6060	5-5a	0.6056
5a-6	0.5355	6-7	0.7372	7-8	0.5863
8-9	0.7368	9-9a	0.5363	9a-10	0.6040
10-10a	0.6112	1-10a	0.5217	4a-10a	0.4859
5a-9a	0.4854	—	—	—	—
Benz[<i>g</i>]isoquinoline (XXIV)					
1-2	0.7220	2-3	0.5731	3-4	0.7412
4-4a	0.5332	4a-5	0.6078	5-5a	0.6051
5a-6	0.5359	6-7	0.7370	7-8	0.5861
8-9	0.7372	9-9a	0.5354	9a-10	0.6060
10-10a	0.6051	1-10a	0.5385	4a-10a	0.4836
5a-9a	0.4849	—	—	—	—
Acridine (XXV)					
1-2	0.7358	2-3	0.5884	3-4	0.7332
4-4a	0.5429	4a-10	0.5853	1-9a	0.5363
9-9a	0.6028	4a-9a	0.4882	—	—

^a See Fig. 9.

Notes Added in Proof

An extensive study has been performed concerning the basicity of aminoazines using the SCF MO LCAO method.¹⁶⁵ Moreover, attention has been paid to the influence of various factors influencing the basicity of azines¹⁶⁶ and to the relationship between the protonation and solvation entropy.¹⁶⁷

Intensities and excitation energies of the L_a bands of eleven azines were computed using the HMO method¹⁶⁸; polarographic half-wave potentials were investigated too.¹⁶⁹ There is a good agreement between the half-wave potentials given in this study and those mentioned in Table IV. Further studies deal with the rate of quaternization,¹⁷⁰ infrared absorption ($1000\text{--}650\text{ cm}^{-1}$),¹⁷¹ and charge-transfer complexes of *N*-methylated azines with polycyclic aromatic hydrocarbons.¹⁷²

Considerable progress has been achieved in the application of the NQR spectroscopy¹⁷³ concerning ^{14}N . The experimentally determined π -electron densities at the nitrogen atoms in pyridine, pyrazine, *sym*-triazine, and phenazine have been compared with those calculated by the MO method on various levels of sophistication. It seems that the experimental results are best explained by the HMO data.

The chemical shifts of H and N in pyridine and the pyridinium cation were interpreted.¹⁷⁴ Qualitative agreement has been obtained between NMR data and calculated π -electron densities for pyridine, quinoline, isoquinoline, and pyrimidine.¹⁷⁵

¹⁶⁵ F. Peradejordi, *Cahiers Phys.* **17**, 453 (1963).

¹⁶⁶ O. Chalvet, R. Daudel, and F. Peradejordi, *J. Chim. Phys.* **59**, 709 (1962).

¹⁶⁷ O. Chalvet, R. Daudel, and F. Peradejordi, *Compt. Rend.* **254**, 1283 (1962).

¹⁶⁸ J. Nasielski and E. Vander Donckt, *Bull. Soc. Chim. Belges* **72**, 725 (1963).

¹⁶⁹ G. Anthoine, G. Coppens, J. Nasielski, and E. Vander Donckt, *Bull. Soc. Chim. Belges* **73**, 65 (1964).

¹⁷⁰ G. Coppens and J. Nasielski, *Bull. Soc. Chim. Belges* **71**, 5 (1962).

¹⁷¹ G. Coppens and J. Nasielski, *Bull. Soc. Chim. Belges* **70**, 136 (1961).

¹⁷² J. Nasielski and E. Vander Donckt, *Theoret. Chim. Acta* **2**, 22 (1964).

¹⁷³ L. Guibé and E. A. C. Lucken, *Ampère Colloquium*, Louvain, September 1964; personal communication.

¹⁷⁴ V. M. S. Gil and J. N. Murrell, *Trans. Faraday Soc.* **60**, 248 (1964).

¹⁷⁵ B. P. Dailey, A. Gawer, and W. C. Neikam, *Discussions Faraday Soc.* No. **34**, 18 (1962).

1,2,4-Thiadiazoles

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I. Introduction

A. HISTORICAL

Although the chemistry of 1,2,4-thiadiazoles is a relatively narrow field, its history touches the very beginnings of organic chemistry as

we know it today, and is in fact associated with its founder. In 1821 F. Wöhler observed that thiocyanic acid decomposed in concentrated solution to give a yellow solid, isoperthiocyanic acid, from which 1,2,4-thiadiazole derivatives were later prepared. The difficult problem of elucidating the structure of isoperthiocyanic and perthiocyanic acids has occupied research workers at intervals since then, and has only very recently been solved satisfactorily. The remarkable oxidation of aromatic thioureas to 1,2,4-thiadiazolidines (the so-called "Hector's bases"), first observed in 1889, posed another structural problem, that is only at the present time being settled. The parent compound of the series, 1,2,4-thiadiazole, was first prepared as late as 1955. The story of the chemistry of the 1,2,4-thiadiazoles, with its very early beginnings and slow start, reflects in a certain measure the rise and increasingly rapid expansion of the science of organic chemistry as a whole.

Because of the greater-than-average difficulties encountered in the study of these heterocycles, the older literature is unusually confused and controversial, a fact that is clearly apparent from Bambas's review¹ of this subject published in 1952. In another survey² of this field, the literature is covered up to 1956. It is probably true that the most rapid and significant progress dates from about 1954. In the present review, an attempt is therefore made to provide a comprehensive account of the development of the chemistry of the 1,2,4-thiadiazoles during the last ten years. To put the advances into perspective, and for the sake of completeness, the older work is very briefly summarized, chiefly in form of references.

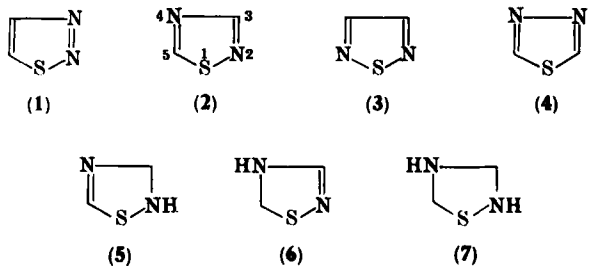
Renewed interest in 1,2,4-thiadiazoles is not merely part of the general intensive activity in contemporary heterocyclic chemistry. It is obviously desirable to compare this ring system with closely related important heterocycles (including thiazoles, oxazoles, pyrimidines, etc.), the chemistry of which is known in much greater detail. The isosteric relationship between pyrimidine and 1,2,4-thiadiazole (but not with any of its isomers) foreshadows similarities in certain physical properties of the two series. The question of the biochemical function and physiological activity of heterocyclic compounds of this general pattern has also served to reinforce interest in the 1,2,4-thiadiazoles.

¹ L. L. Bambas, "Five-Membered Heterocyclic Compounds," p. 35 *et seq.* Interscience, New York, 1952.

² W. A. Sherman, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 7, p. 558 *et seq.* Wiley, New York, 1961.

B. NOMENCLATURE AND STRUCTURE

Of the four possible isomeric thiadiazoles (1-4), the 1,3,4-isomers (4) are by far the best-known.^{1, 2} The 1,2,4-thiadiazole nucleus is numbered as in 2; the nomenclature of the partly hydrogenated forms, Δ^4 -thiadiazolines (5) and Δ^2 -thiadiazolines (6), and the fully reduced thiadiazolidine (7) follows the usual rules. In the older literature, 1,2,4-thiadiazoles are occasionally indexed as azosulfimes or as perthiocyanates.



By virtue of the nature of the atoms in its ring system and the number and position of its double bonds, 1,2,4-thiadiazole possesses aromatic character and is classified, according to Albert,³ as a π -excessive sulfur-containing heteroaromatic compound.

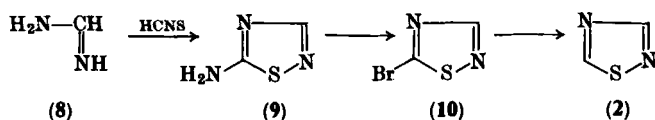
A mathematical analysis of all four isomeric thiadiazoles by the simple molecular orbital method has provided molecular diagrams of the free base and conjugate acid of each thiadiazole, with electron densities, bond orders, and free valencies. On this basis, predictions have been made concerning the reactivities of the six non-equivalent carbon atoms, the basicities of the nitrogen atoms, and the delocalization energies in these molecules. The 5-position in free 1,2,4-thiadiazole should possess maximum reactivity in nucleophilic substitution reactions. The treatment also accounts for the order of the polarographic half-wave potentials and the position of the absorption maxima in the ultraviolet region of the spectra of 1,2,4- and 1,3,4-thiadiazoles.⁴

³ A. Albert, "Heterocyclic Chemistry." Athlone Press, London, 1959.

⁴ R. Zahradník and J. Koutecký, *Collection Czech. Chem. Commun.* **26**, 156 (1961).

II. Synthesis of 1,2,4-Thiadiazoles

No naturally occurring 1,2,4-thiadiazole having been reported so far, all compounds are of synthetic origin. The parent of the series, 1,2,4-thiadiazole, was first synthesized in 1955⁵ by the sequence of reactions $8 \rightarrow 9 \rightarrow 10 \rightarrow 2$,^{5,6} but remains relatively inaccessible. Because of its sensitivity it is not a practicable starting material for the preparation of derivatives; these are therefore always built up directly by suitable cyclization reactions and subsequent modification of the substituents as required. This section is confined to direct syntheses: the numerous interconversions that furnish additional derivatives from the pre-formed 1,2,4-thiadiazole nucleus are considered with the chemical properties of the individual classes of compounds.



The 1,2,4-thiadiazole ring (2) may obviously be built up from simpler fragments in many ways, but of these only three general routes are important: these approaches, classified according to the nature of the components which join to form the ring, are illustrated by A-C. A



number of syntheses that cannot be fitted obviously into these schemes are dealt with separately.

A. TYPE A SYNTHESSES



This group of syntheses comprises the oxidation of compounds containing the thiocarbamoyl group, including thioamides and thioureas;

⁵ J. Goerdeler, J. Ohm, and O. Tegtmeier, *Chem. Ber.* **89**, 1534 (1956); J. Goerdeler and O. Tegtmeier, *Angew. Chem.* **67**, 302 (1955).

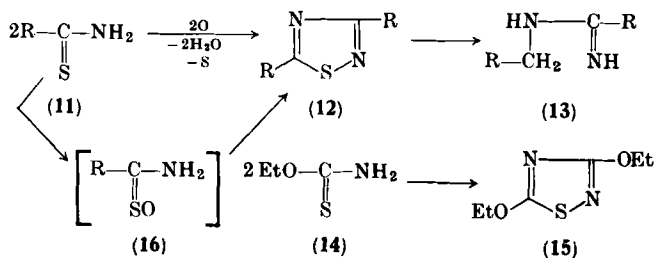
⁶ J. Goerdeler, K. Wember, and G. Worsch, *Chem. Ber.* **87**, 57 (1954).

these compounds show a remarkable tendency to give rise to the 1,2,4-thiadiazole system on oxidation under certain conditions.

The inclusion of reactions under this heading is convenient merely for the purpose of formal classification; it is not intended to suggest the mechanism by which the thiadiazoles arise. Present trends indicate that these routes proceed by way of intermediates that will eventually justify their classification as syntheses of type C.

1. Oxidation of Thioamides

a. *Oxidizing Agents.* The action of a variety of oxidizing agents⁷ on thioamides (11) yields 3,5-disubstituted 1,2,4-thiadiazoles (12). Much of the published work concerns thiobenzamide; Hofmann⁸ oxidized this compound by means of iodine in 1869 and assigned⁹ the correct structure (12; R = Ph) to it on the basis of its non-identity with 2,5-diphenyl-1,3,4-thiadiazole and its reduction to *N*-benzylbenzamidine (13; R = Ph).⁹ This formulation is now firmly established by the alternative unequivocal synthesis from thiobenzoyl-benzamidine (see Section II, C, 1).



Other oxidizing agents that have been successfully employed are sulfur monochloride,^{10, 11} thionyl chloride,¹² sulfuryl chloride,¹² phosphorus pentachloride,¹³ ammonium persulfate,¹⁴ hydrogen peroxide,¹⁵

⁷ P. Chabrier and S. H. Renard, *Bull. Soc. Chim. France* D 272 (1949).

⁸ A. W. Hofmann, *Ber.* **2**, 645 (1869).

⁹ A. W. Hofmann and S. Gabriel, *Ber.* **25**, 1578 (1892).

¹⁰ S. Ishikawa, *Sci. Papers Inst. Phys. Chem. Res. (Tokyo)* **3**, 147 (1925).

¹¹ G. C. Chakravarti, *J. Chem. Soc.* **123**, 964 (1923).

¹² S. Ishikawa, *Sci. Papers Inst. Phys. Chem. Res. (Tokyo)* **7**, 237 (1928).

¹³ A. V. Kirsanov and V. A. Shokol, *Zh. Obshch. Khim.* **30**, 3031 (1960).

¹⁴ R. von Walther, *J. Prakt. Chem.* **69**, 44 (1904).

¹⁵ R. Kitamura, *J. Pharm. Soc. Japan*, **58**, 809 (1938).

ozone,^{7, 16} nitrous acid in various solvents,^{17, 18} *N,N*-dichloromethyl carbamate (ROCONCl₂), sodium *N*-chloromethyl carbamate,¹⁹ and 2-bromoindane-1,3-dione.²⁰ Chlorine, bromine, and nitric acid are less suitable, because they tend to cause simultaneous substitution reactions to occur.⁸

The reaction has been extended to the preparation of other 3,5-diaryl (and alkyl)-1,2,4-thiadiazoles²¹⁻²³ and to diheteryl analogs, including 3,5-difuryl²⁴ and 3,5-di-(3-[or 4]-pyridyl)-1,2,4-thiadiazoles.^{19, 24} Xanthamide (14) similarly yields 3,5-diethoxy-1,2,4-thiadiazole (15).^{25, 26}

The oxidation of *N*-acetylthiourea in pyridine by hydrogen peroxide to the diacetyl derivative of 3,5-diamino-1,2,4-thiadiazole (12, R = AcNH) (in 35% yield)²⁷ may also be included under this general heading.

b. *The Use of Hydrogen Peroxide. Thioamide-S-oxides.* In the oxidation of thioamides by hydrogen peroxide, Kitamura¹⁵ succeeded in isolating unstable intermediate *S*-oxides (named by him "thioperimidic acids"). The phenyl homolog (16; R = Ph) is changed under the influence of light, or on being heated by itself or with water, or on treatment with thiobenzamide, into benzonitrile and 3,5-diphenyl-1,2,4-thiadiazole.¹⁵

3,5-Dialkyl(or aryl) analogs with unlike substituents are obtainable by this last route: thus, treatment of phenylthioacetamide-*S*-oxide (17) with thiobenzamide (18) gave a product that was formulated as 5-benzyl-3-phenyl-1,2,4-thiadiazole (19),¹⁵ but was recently recognized²⁸ to be the 3-benzyl-5-phenyl isomer 21. It does not, therefore, arise by

¹⁶ R. Kitamura and Y. Katoh, *Sci. Rept. Tokyo*, **2**, 17 (1932).

¹⁷ M. W. Cronyn and T. W. Nakagawa, *J. Am. Chem. Soc.* **74**, 3693 (1952).

¹⁸ H. Krall and V. Sagar, *J. Indian Chem. Soc.* **17**, 475 (1940).

¹⁹ P. Chabrier, S. H. Renard, and K. Smarzewska, *Bull. Soc. Chim. France* **237** (1949).

²⁰ C. L. Arcus and G. C. Barrett, *J. Chem. Soc.* 2098 (1960).

²¹ A. Bernthsen, *Ann. Chem.* **184**, 290 (1877).

²² R. Wanstrat, *Ber.* **6**, 332 (1873).

²³ A. Reissert and F. Grube, *Ber.* **42**, 3710 (1909).

²⁴ R. I. Meltzer, A. D. Lewis, and J. A. King, *J. Am. Chem. Soc.* **77**, 4062 (1955).

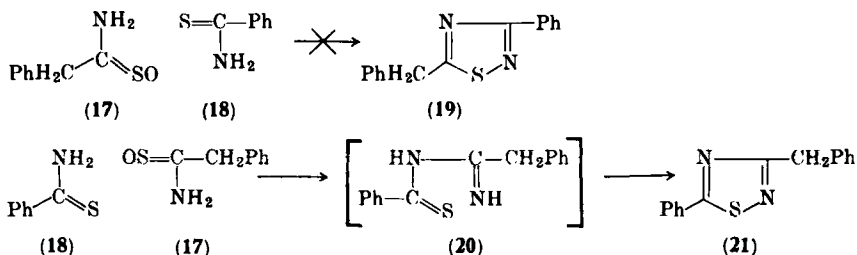
²⁵ B. Holmberg, *Svensk Kem. Tidskr.* **41**, 249 (1929).

²⁶ J. V. Dubský and J. Trtlík, *Chem. Obzor.* **8**, 1 (1933); *Chem. Abstr.* **27**, 2137 (1933).

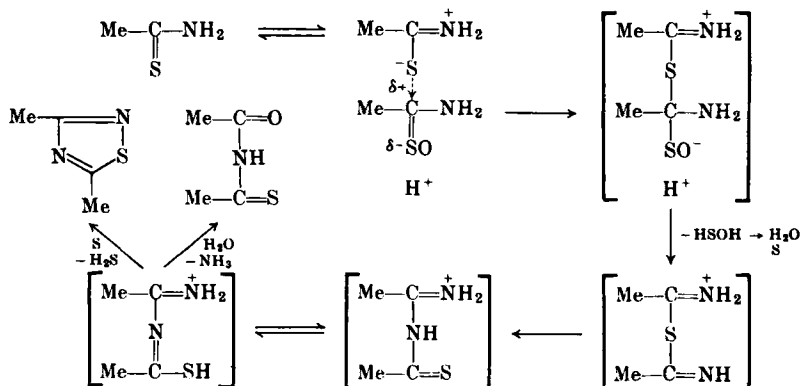
²⁷ W. Walter, *Angew. Chem.* **70**, 371 (1958).

²⁸ J. Goerdeler and H. Porrmann, *Chem. Ber.* **95**, 627 (1962).

the originally suggested condensation¹⁵ ($17 + 18 \rightarrow 19$), but the *S*-oxide appears to act merely as an imidoacylating agent, yielding the intermediate thioacylamidine **20** (with loss of $-\text{SOH}$) and thence the 1,2,4-thiadiazole **21**.²⁸



The nature of thioamide-*S*-oxides and their role in the formation of 1,2,4-thiadiazoles have recently been studied in detail by Walter and his co-workers.^{27, 29-32} Treatment of thioacetamide at -30 to -10° with perhydrol saturated with ammonium sulfate furnishes a 58% yield of crystalline thioacetamide-*S*-oxide, which if pure may be kept almost indefinitely at 0° .²⁹ Thioformamide-*S*-oxide, the parent compound of this series, is even more stable than the methyl homolog.³¹ The reaction between thioacetamide-*S*-oxide and thioacetamide proceeds less readily than that involving the aromatic analogs: in dilute sulfuric acid at room temperature, *N*-acetylthioacetamide (6%) is



²⁹ W. Walter, *Ann. Chem.* **633**, 35 (1960).

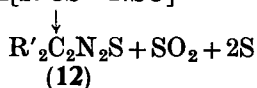
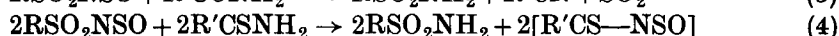
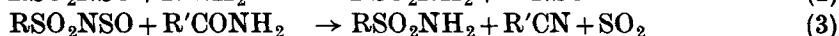
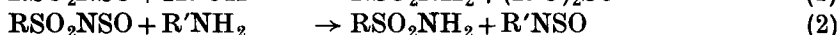
³⁰ W. Walter, *Ann. Chem.* **633**, 49 (1960).

³¹ W. Walter and J. Curts, *Chem. Ber.* **93**, 1511 (1960).

³² W. Walter, J. Curts, and H. Pawelzik, *Ann. Chem.* **643**, 29 (1961).

formed; at 120–125° direct interaction produces 3,5-dimethyl-1,2,4-thiadiazole, also in low yield.³⁰ The detailed mechanism shown (foot of p. 125) has been proposed³⁰ to account for the observations and is also applicable, in its essentials, to the formation of the aromatic analogs.

In a systematic study of the chemistry of *N*-sulfinylamines ($R-N=SO$), Kresze and his co-workers³³ demonstrated the outstanding reactivity of the closely related *N*-sulfinylsulfonamides ($RSO_2N=SO$). Their initial sulfinylating action [e.g. on alcohols and amines, Eqs. (1) and (2)] may be followed by immediate further reaction. Thus, amides yield nitriles [Eq. (3)], while both aromatic and aliphatic thioamides are converted into 3,5-disubstituted 1,2,4-thiadiazoles [Eq. (4)] in satisfactory yields.



2. Oxidation of Aromatic Thioureas

a. *Monoarylthioureas*. Depending on the nature of the reagent and the conditions, thioureas on oxidation are converted into a variety of products, including disulfides, *S*, *S*-dioxides, benzothiazoles, and thiadiazoles. Treatment of *N*-monoarylthioureas with oxidizing reagents in ionizing media, preferably in an acidic environment, yields a series of substituted 1,2,4-thiadiazolidines, which are known, after their discoverer, as "Hector's bases."^{34–36} The cyclization, involving two molecules of the aromatic thioureas, generally proceeds remarkably readily in good yield and may be performed by means of a variety of oxidizing reagents (see Table I). Diaryldithioformamidine salts (22) have also been used as starting materials.^{37, 38}

³³ G. Kresze, A. Maschke, R. Albrecht, K. Bederke, H. P. Patzschke, H. Smalla, and A. Tredø, *Angew. Chem.* **74**, 135 (1962).

³⁴ D. S. Hector, *Ber.* **22**, 1176 (1889).

³⁵ D. S. Hector, *Ber.* **23**, 357 (1890).

³⁶ D. S. Hector, *Ber.*, *Referate* **25**, 799 (1892); *Öfversigt af Kongl. Vet.-Akad. Förh.* No. 2, 79 (1892).

³⁷ G. Mazzone, *Boll. Sedute Accad. Gioenia Sci. Nat. Catania* [4], **6**, 631 (1960); *Chem. Abstr.* **58**, 6829 (1963).

³⁸ K. S. Suresh, *J. Sci. Research Banaras Hindu Univ.* **9**, 94 (1959); *Chem. Abstr.* **54**, 22429 (1960).

The production and structure of "Hector's bases" have been the subjects of previous summaries^{1, 2} and need not therefore be discussed in detail here. Recent results appear to favor their representation as 4-aryl-3-arylimino-5-imino-1,2,4-thiadiazolidines (35)^{53, 54a}

(i) *The structure of Hector's bases.* The formulation of Hector's bases^{54b} as 1,2,4-thiadiazolidines has long been based with reasonable

TABLE I
OXIDATION OF ARYLTHIOUREAS

Oxidizing reagent	References
Hydrogen peroxide, 6%	34-36, 39, 40
Hydrogen peroxide, 30%	37, 40, 41
Nitrous acid	34, 42-45
Ferric chloride	34, 46
Cupric salts	46-48
Iodine, alcoholic or aqueous	34, 46
Bromine, alcoholic	49
Toluene- <i>p</i> -sulfonyl chloride	50, 51
Oxygen, in presence of carbon	52

³⁹ K. B. Lal and H. Krall, *J. Indian Chem. Soc.* **16**, 31 (1939).

⁴⁰ F. Kurzer and P. M. Sanderson, *J. Chem. Soc.* 1058 (1959).

⁴¹ F. Kurzer and P. M. Sanderson, *J. Chem. Soc.* 4461 (1957).

⁴² R. Sahasrabudhey and H. Krall, *J. Indian Chem. Soc.* **22**, 37 (1945).

⁴³ K. B. Lal and H. Krall, *J. Indian Chem. Soc.* **15**, 217 (1938).

⁴⁴ S. Mehta and H. Krall, *J. Indian Chem. Soc.* **12**, 640 (1935).

⁴⁵ J. Haager and R. Doht, *Monatsh. Chem.* **27**, 267 (1906).

⁴⁶ R. Sahasrabudhey and H. Krall, *J. Indian Chem. Soc.* **19**, 25 (1942).

⁴⁷ R. Sahasrabudhey and H. Krall, *J. Indian Chem. Soc.* **21**, 67 (1944).

⁴⁸ K. B. Lal and H. Krall, *J. Indian Chem. Soc.* **14**, 474 (1937).

⁴⁹ A. Hugershoff, *Ber.* **34**, 3130 (1901).

⁵⁰ E. Fromm and R. Heyder, *Ber.* **42**, 3804 (1909).

⁵¹ K. S. Suresh and P. Mukherjee, *Vikram, J. Vikram Univ.* **2**, 127 (1958); *Chem. Abstr.* **54**, 5627 (1960).

⁵² H. Freundlich and A. Bjerke, *Z. Physik. Chem.* **91**, 1 (1916).

⁵³ C. P. Joshua, V. K. Verma, and K. S. Suresh, *Tetrahedron Letters* 663 (1961).

^{54a} F. Kurzer and P. M. Sanderson, *J. Chem. Soc.* 3336 (1963); *Chem. Ind. (London)* 1681 (1962).

^{54b} In the following discussion, the term "Hector's base" refers to the phenyl homolog unless otherwise stated.

probability on the parallel oxidation, under comparable conditions, of thioamides to 1,2,4-thiadiazoles (see Section II, A, 1) and was not disproved by their chemical behavior (see below). Accepting this heterocyclic structure, it remained to distribute correctly arylimino, aryl, or imino groups in this system. Of the six possible structures (31–36) which have been considered by various investigators (e.g. 31⁹, 32,⁵⁶ 34⁵⁹), three may now be eliminated from the outset for the following reasons: the non-identity of Hector's base with the oxidation product of authentic *N*-phenyl-*N'*-phenylamidinothiourea (25)^{56, 57a} excludes structures 31 and 32. The demonstrated near-quantitative reduction of Hector's bases to *s*-diarylguanidines^{34–36, 53, 55} rules out structures 31, 32, and 33. Of the remaining possibilities, structure 36, originally chosen by the discoverer of these compounds, has been used most consistently and has generally been employed in indexing them in the literature.

More decisive evidence is provided by the interconvertibility of *N*-aryl-*N*-arylamidinothioureas (28) and Hector's bases by oxidation-reduction.^{53, 54, 57b} The former compounds are accessible (as salts) (i) by the condensation of arylthioureas (24) with arylcyanamides (23),⁵³ (ii) by the extrusion of sulfur from the recently described^{40, 41} *s*-diaryldithioformamidine hydrobromides^{54a} (22), (iii) by the oxidation of arylthioureas (24) with 0.5 moles of hydrogen peroxide in the presence of mineral acids,^{54a} and (iv) by the mild reduction of Hector's bases by hydrogen sulfide in acid media.^{54a} The first of these four reactions limits the structure of the products to the three alternatives 25, 28, and 30. Of these, 25 is excluded by the non-identity of the product with authentic^{57a} *N*-phenyl-*N'*-phenylamidinothiourea (25; R = Ph). The monosulfide structure (30) is not reconciled as readily with the observed^{54a} hydrolytic fission of the products into diarylguanidines (29) and thiocyanic acid as is structure 28. Indeed, as in the case of thioamides and nitriles (see Section II, C, 1), the present condensation may involve the primary formation of an intermediate diimido-monosulfide (30) and its isomerization to 28.

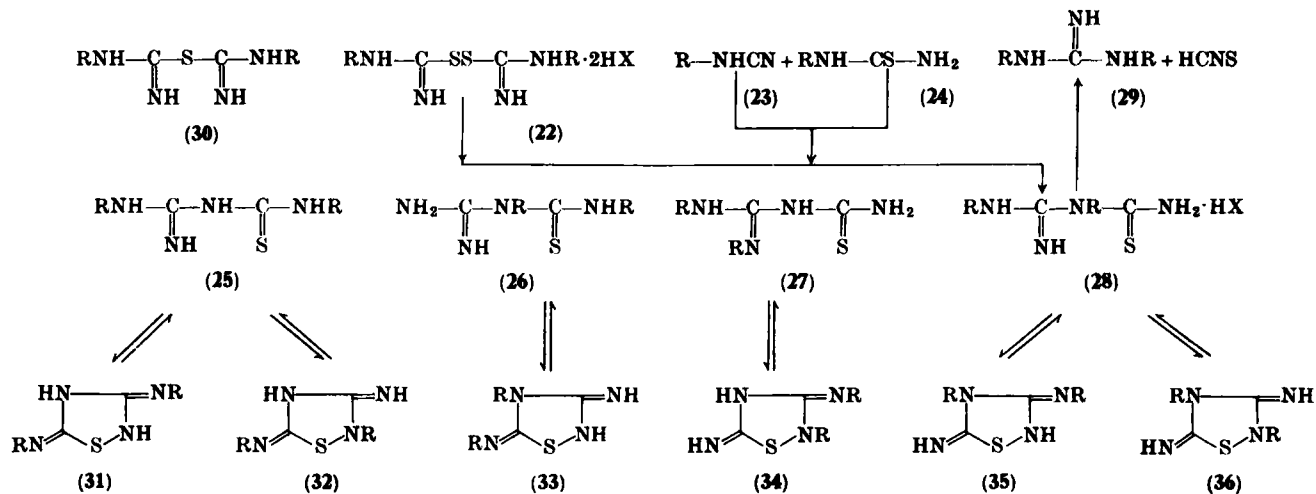
The ready oxidation^{53, 54} of *N*-aryl-*N*-arylamidinothioureas (28) to

⁵⁵ K. Dost, *Ber.* **39**, 863 (1906).

⁵⁶ F. Kurzer, *J. Chem. Soc.* 2345 (1956).

^{57a} F. Kurzer, *Chem. Ind. (London)* 526 (1956); F. Kurzer and P. M. Sanderson, *J. Chem. Soc.* 3333 (1963).

^{57b} This reaction should be properly classified amongst type-C syntheses (Section II, C), but it is included here to provide a unified structural account.



Hector's bases^{57b} thus leaves a choice between **35** and **36** for the structure of the latter. The decision in favor of **35** is based on the assumption that a free amino group rather than the anilino group is likely to be involved in the ring closure (**28** → **35**); it is supported by the fact that the chemical properties of Hector's bases are accounted for better in terms of structure **35** than **36** (see below).

The connection between diaryldithioformamidines (**22**) and Hector's bases thus established suggests that the production of these heterocyclic bases from aromatic thioureas proceeds in acid media by way of primarily formed dithioformamidines (for references, see ref. 41) by the following sequence: **24** → **22** → (**23** + **24**) → **28** → **35**. In particular, this interpretation accounts for the contrasting course of the oxidation of arylthioureas to Hector's bases in acidic polar solvents where intermediate disulfide formation is favored, and to benzthiazoles⁵⁸ in non-polar neutral solvents where a free-radical mechanism may operate.

(ii) *Properties of Hector's bases.* Except for their reduction, which may be accounted for equally well in terms of structures **35** and **36**, the chief chemical properties of Hector's bases are reflected more accurately by the 4-aryl-3-arylimino-5-imino-1,2,4-thiadiazolidine structure (**35**).

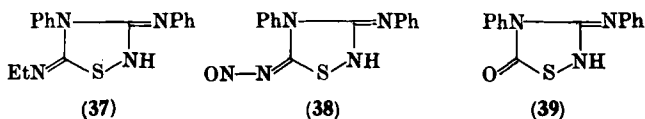
Reduction. The near-quantitative reduction of Hector's bases to *s*-diarylguanidines under various conditions^{34-36, 53, 55} is well established. Milder reduction, by hydrogen sulfide at 25°, gives excellent yields of *N*-aryl-*N*-arylamidinothioureas (**28**),^{54a} obviously by the familiar preferential fission of the heterocycle at the S—N(2) bond (see Section III,D,1); since these amidinothioureas (**28**) are cleaved to *s*-diarylguanidines and thiocyanic acid under the mildest hydrolytic conditions,^{54a} their primary formation in *all* reductions of Hector's bases is probable.^{54a}

Acidity. Hector's bases are mono-acid bases^{34-36, 40, 41, 50, 51}; the presence of only one imino group in the preferred formulation **35** accounts well for the observed exclusive formation of monoalkyl, monoacyl, and mononitroso derivatives. The *N*-ethyl derivative³⁶ is reducible to *s*-diphenylguanidine and ethylamine and is therefore regarded^{54a} as **37**, and the nitroso derivative as **38**.

Dost's keto compound. Treatment with concentrated hydrochloric acid converts Hector's base into a non-basic keto compound⁵⁵; this is

⁵⁸ J. M. Sprague and A. H. Land, in "Heterocyclic Compounds" (R. C. Elderfield, ed.) Vol. 5, p. 542 *et seq.* Wiley, New York, 1957.

also reducible to *s*-diphenylguanidine, but no longer yields acyl derivatives,⁵⁵ and is represented as **39**.^{54a}



Isomerization. Treatment of Hector's bases with ethanolic ammonia at 150°^{55, 57a} yields products that were originally indexed arbitrarily as 1,4-diaryl-5-imino-3-thiono-1,2,4-triazolidines⁵⁹ but have been identified as 3,5-di-(arylamino)-1,2,4-thiadiazoles (**31**).^{57a} This isomerization resembles the well-documented analogous reaction of 5-imino-4-methyl-1,2,4-thiadiazoline (see Section III, D, 1) and thus proceeds by ring opening at C(3)—N(4), followed by exchange of the =NH and —NPh groups by rotation about the S—C(5) bond. This isomerization is represented more simply in terms of structure **35** than **36**. Whatever the mechanism, the former requires the displacement of only one aryl group, while the latter presupposes two such changes.

b. *N,N'*-Diarylthiourreas. The oxidation of *N,N'*-diarylthiourreas by hydrogen peroxide^{35, 60} or alcoholic bromine^{61, 62} yields products that were originally represented as 2,4-diaryl-3,5-di-(arylimino)-1,2,4-thiadiazolidines (**40**); much of this work, however, has recently been disproved.⁶³⁻⁶⁶

The compound (m.p. 136°) obtained from *N,N'*-diphenylthiourea is in fact^{63, 64} 1-(benzthiazol-2'-yl)-1,2,3-triphenylguanidine (**43**) as suggested by its infrared and ultraviolet spectra^{65a} and shown by its independent synthesis from 2-anilinobenzthiazole (**44**) and diphenylcarbodiimide.⁶⁴ Its degradation to *s*-triphenylguanidine and 2-amino-benzthiazole derivatives⁶² (see also ref. 63) are thus accounted for.

Under restrained conditions, the oxidation of *N,N'*-diphenylthiourea by bromine (approximately 2 moles) may be terminated at an

⁵⁹ Beilstein's "Handbuch," Hauptwerk, 4th Ed., 1937, Vol. 27, pp. 661, 663.

⁶⁰ T. Chakrabarti and S. De, *J. Indian. Chem. Soc.* **5**, 661 (1928).

⁶¹ A. Hegershoff, *Ber.* **36**, 3121 (1903).

⁶² E. Fromm and W. Bitterich, *Ann. Chem.* **394**, 284 (1912).

⁶³ K. S. Suresh, *J. Indian Chem. Soc.* **37**, 25, 483 (1960).

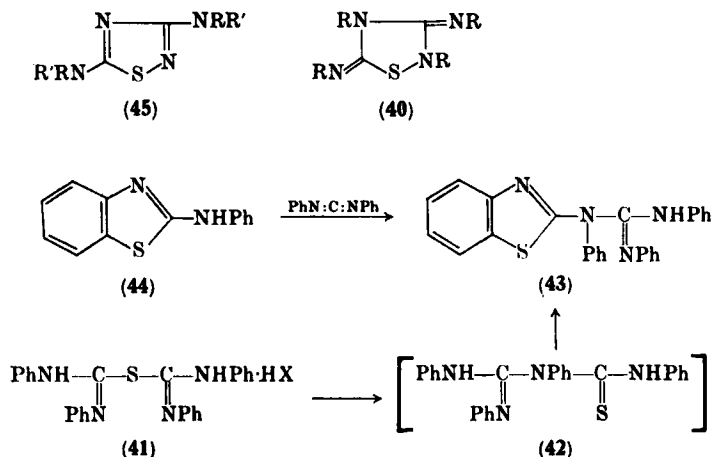
⁶⁴ V. K. Verma and K. M. Sarkar, *J. Sci. Ind. Res. (India)* **21B**, 236 (1962).

^{65a} K. S. Suresh and C. N. R. Rao, *J. Indian Chem. Soc.* **37**, 581 (1960).

^{65b} The authors⁶⁰ represented their products as 1,3,4-thiadiazolidines, without giving reasons for this formulation.

⁶⁶ K. S. Suresh, *J. Indian Chem. Soc.* **35**, 170 (1958).

intermediate stage: the isolated hydrobromide has been formulated as tetraphenylformamidine monosulfide (41)⁶³; its further oxidation with bromine yields again 1-(benzthiazol-2'-yl)-1,2,3-triphenylguanidine (43). It would be interesting to establish whether the intermediate salt is in fact the substituted guanidine 42, arising from the primary monosulfide by the usual isomerization (see Section II, C, 1); its oxidation to the substituted benzthiazole 43 would follow directly.



A number of thiadiazolidines supposedly obtained by Chakrabarti and De^{60, 65b} by the action of alcoholic hydrogen peroxide on *N,N'*-diarylthioureas (in the absence of acids) have proved to be merely the corresponding *N,N'*-diarylureas.⁶⁶

c. *N,N*-Disubstituted Thioureas. *N,N*-Diarylthioureas⁶⁰ and *N*-alkyl-*N*-arylthioureas^{9, 42, 60, 63, 66, 67a} when oxidized (by nitrous acid⁴² or hydrogen peroxide^{9, 60, 63, 66, 67a}) yield products to which the 3,5-di-(alkylaryl-[or diaryl]-amino)-1,2,4-thiadiazole structure⁴⁵ has been assigned.^{67b} Support for this formulation is provided⁶³ by the close resemblance of the ultraviolet absorption spectrum of the oxidation product from *N*-methyl-*N*-phenylthiourea to that of authentic⁶⁶ 3,5-dianilino-1,2,4-thiadiazole (see also ref. 65a for infrared absorption data).

^{67a} K. B. Lal and H. Krall, *J. Indian Chem. Soc.* **14**, 478 (1937).

^{67b} The corresponding 1,3,4-thiadiazole structure has been assumed, without further evidence, by Chakrabarti and De.⁶⁰

The product obtained⁶⁸ by the action of methylaniline on methyl-phenylthiuret has proved identical with the oxidation product of *N*-methyl-*N*-phenylthiourea⁶³ and is therefore also formulated as **45** ($R = \text{Ph}$, $R' = \text{Me}$).

B. TYPE B SYNTHESSES



The second group of syntheses comprises those cyclizations which involve a two-stage condensation between a compound incorporating an amidino group [including amidoximes, amidines, iso(thio)ureas, guanidines, etc.] and one containing a thiocarbonyl group (e.g. carbon disulfide, thiocyanogen, thiocyanate, isothiocyanate esters, and halogenated methanesulfonyl chlorides). Recent contributions have made this a remarkably versatile approach to 1,2,4-thiadiazoles.

1. Syntheses from Amidoximes

Amidoximes (**46**) were first used as a source of 1,2,4-thiadiazoles in 1889; their condensation with carbon disulfide or with an excess of aryl isothiocyanate yields 3-aryl-5-mercapto- (**47**)⁶⁹⁻⁷³ or 3-aryl-5-aryl-amino-1,2,4-thiadiazoles (**50**),^{71, 74, 75} respectively. The latter reaction has been reexamined and discussed by Gheorgiu and Barbos⁷⁵ who suggest that an initial addition of two moles of phenyl isothiocyanate to one of benzamidoxime is followed by cyclization of the intermediate (**49**), with elimination of phenylthiocarbamic acid (**51**). Decomposition of the latter gives rise to the by-products observed (cf. following scheme).

The conversion of 5-amino-3,5-diphenyl-1,2,4-oxadiazoline (**48**) into 5-mercapto-3-phenyl-1,2,4-thiadiazole (**47**)⁷⁶ under the influence

⁶⁸ E. Fromm and H. Baumhauer, *Ann. Chem.* **361**, 319 (1908).

⁶⁹ F. Tiemann, *Ber.* **22**, 2391 (1889).

⁷⁰ L. H. Schubart, *Ber.* **22**, 2441 (1889).

⁷¹ F. Tiemann, *Ber.* **24**, 369 (1891).

⁷² G. Crayen, *Ber.* **24**, 385 (1891).

⁷³ E. J. Birr, German Patent 950,537 (1956); *Chem. Abstr.* **53**, 17737 (1959).

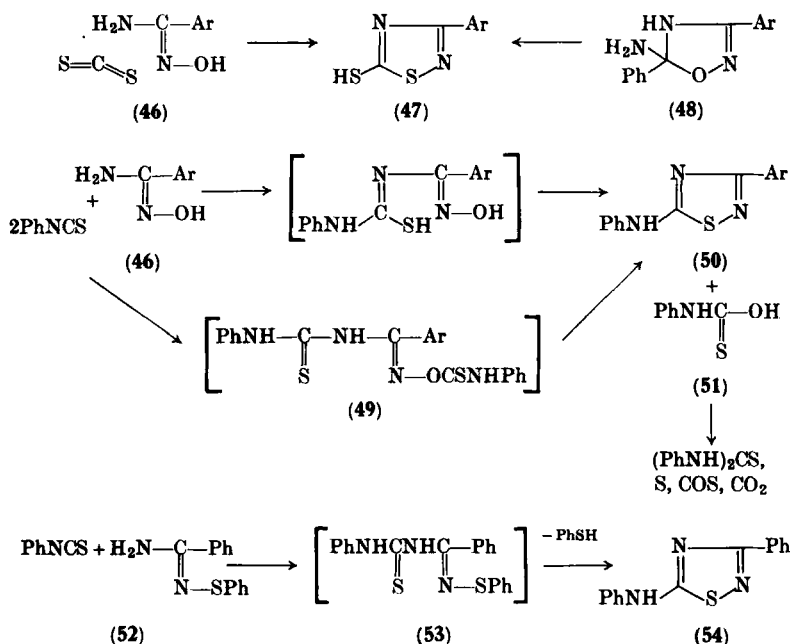
⁷⁴ H. Koch, *Ber.* **24**, 394 (1891).

⁷⁵ C. V. Gheorgiu and A. Barbos, *Ann. Sci. Univ. Jassy* **26**, 271 (1940).

⁷⁶ J. Stieglitz, *Ber.* **22**, 3148 (1889).

of carbon disulfide at 100° probably involves the intermediate formation of benzamidoxime; the latter is known to arise from the oxadiazoline on heating and would then react with the carbon disulfide in the usual way.

The interaction of the recently discovered *N*-(benzenesulfonyl)-benzamidine (52) and phenyl isothiocyanate yields 5-anilino-3-phenyl-1,2,4-thiadiazole (54), probably by a route (52 → 53 → 54) that may thus be classified under the present heading.⁷⁷



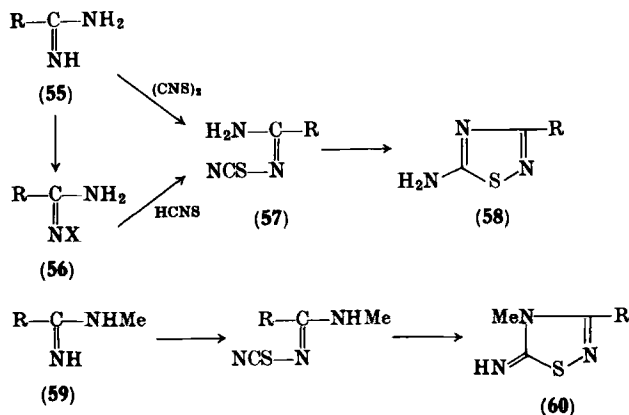
2. Syntheses from Amidines

In 1954, Goerdeler⁶ introduced a general synthesis of 1,2,4-thiadiazoles from amidines. This versatile method has since been widely extended and has made a great variety of 1,2,4-thiadiazole derivatives readily accessible. Basically, an amidine is converted into its *N*-thiocyanato derivative, which cyclizes spontaneously to the 5-amino-1,2,4-thiadiazole.

⁷⁷ J. Goerdeler, D. Krause-Loevenich, and B. Wedekind, *Chem. Ber.* **90**, 1638 (1957).

Thus, free amidines (55), on treatment with dithiocyanogen,^{6, 78, 79} yield the 1,2,4-thiadiazoles (58) directly; the procedure is limited, however, by the inconvenience of employing the free amidine base (only half of which is in fact utilized in the reaction) and the sensitivity and relative instability of dithiocyanogen.⁶

The scope of the synthesis is greatly widened by the preliminary preparation of the *N*-halogenoamidines (56), preferably *in situ*; subsequent displacement of halogen by thiocyanate results in the formation of the desired 5-amino-1,2,4-thiadiazoles (58) in good yields (50–80%).^{6, 79, 80} The use of formamidine affords the parent, 5-amino-1,2,4-thiadiazole (58; R = H) while use of *N*-methylformamidine (59) leads to 5-imino-4-methyl- Δ^4 -1,2,4-thiadiazolines (60).⁸¹



Intramolecular cyclizations involving amino and thiocyano groups favorably placed sterically in relation to each other are well known and are responsible for the formation of numerous thiazole derivatives.⁸² The special feature of the present synthesis, however, is the attachment of the thiocyanate group at a nitrogen instead of a carbon atom, which seems to enhance its reactivity.

By employing suitable analogs of amidines in this general synthesis,

⁷⁸ J. Goerdeler, *Angew. Chem.* **62**, 341 (1950).

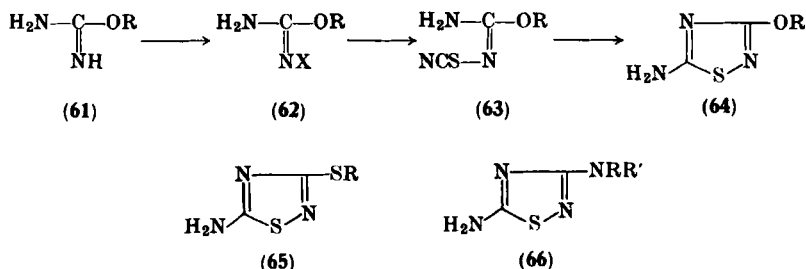
⁷⁹ J. Goerdeler, German Patent 842,346 (1952); *Chem. Abstr.* **52**, 9220 (1958); J. Goerdeler and G. Worsch, German Patent 955,684 (1957); *Chem. Abstr.* **53**, 4306 (1959).

⁸⁰ J. Goerdeler, H. Haubrich, and J. Galinke, *Chem. Ber.* **93**, 397 (1960).

⁸¹ J. Goerdeler, A. Huppertz, and K. Wember, *Chem. Ber.* **87**, 68 (1954).

⁸² A. Schöberl, M. Kawohl, and R. Hamm, *Chem. Ber.* **84**, 571 (1951).

other 3-substituted 5-amino-1,2,4-thiadiazoles are readily accessible. Thus, isoureas (61) furnish, by way of their *N*-halogenated derivatives (62) (which may be isolated in the majority of cases), 3-alkoxy- (or aryloxy)-5-amino-1,2,4-thiadiazoles (64)^{83, 84} in 40–90% yields. Detailed experiments⁸³ with *N*-chloromethylisourea (62; X = Cl, R = Me) suggest that the initial replacement of *N*-halogen by thiocyanate is rapid and is followed by a slower cyclization process; the latter is strongly influenced by the prevailing hydrogen ion concentration, with an optimum at pH 3, probably because only under weakly acid conditions is the cyclization rate high enough to compete successfully with hydrolytic and redox side-reactions.



Isothioureas similarly give, in neutral media, the corresponding 3-alkylthio-5-amino-1,2,4-thiadiazoles (65) in yields exceeding 70%.^{84–86} However, the attempted preparation of the parent 5-amino-3-mercapto-1,2,4-thiadiazole from thiourea or dithioformamide by this route yielded only intractable mixtures.⁸⁵

Further extension of this synthesis to guanidines leads to 3,5-diamino-1,2,4-thiadiazoles. Examples are so far confined to the conversion, by the usual procedure, of *N,N*-disubstituted guanidines into 5-amino-3-dialkyl(or diphenyl)amino-1,2,4-thiadiazoles (66).^{84, 87} In general, this variant of the reaction proceeds less uniformly than with amidines or iso(thio)ureas, and is performed without isolation of the intermediate *N*-halogenoguanidines. In some cases (e.g. dimethyl and cyclopentamethylene homologs) the yields are low, and guanidine is formed as a by-product. The 3-dimethylamino homolog (66; R = R')

⁸³ J. Goerdeler and F. Bechlars, *Chem. Ber.* **88**, 843 (1955).

⁸⁴ J. Goerdeler, M. Lausberg, F. Bechlars, and P. Linden, German Patent 959,191 (1957); *Chem. Abstr.* **53**, 8166 (1959).

⁸⁵ J. Goerdeler and P. Linden, *Chem. Ber.* **89**, 2742 (1956).

⁸⁶ J. Goerdeler and H. Rachwalsky, *Chem. Ber.* **93**, 2190 (1960).

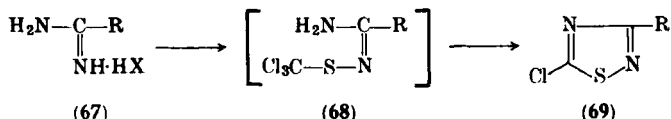
⁸⁷ J. Goerdeler and M. Willig, *Chem. Ber.* **88**, 1071 (1955).

= Me) is best obtained by direct action of dithiocyanogen on the guanidine.⁸⁷

3. Syntheses from Amidino Compounds and Halogenated Methylmercaptans

A further general synthesis, resulting in 3-substituted 5-chloro-1,2,4-thiadiazoles, has been found by Goerdeler⁸⁸ and his co-workers in the action of halogenated methylmercaptans on compounds incorporating an amidino group.

a. *Trichloromethanesulphenyl Chloride* ("Perchloromethylmercaptan") $\text{Cl}_3\text{C}-\text{SCl}$. Amidine salts (67) and trichloromethanesulphenyl chloride in alkali at 0° afford 40–70% yields of 5-halogeno-1,2,4-thiadiazoles (69),^{88, 89} the structures of which are confirmed by their conversion, by ammonia, into the known 5-amino analogs.



This reaction is noteworthy for the fact that one chlorine atom of the reagent remains attached to its carbon atom; usually either *one* or *all* halogen atoms are affected. The reaction sequence of the cyclization (initial S—N or C—N addition) is not established, since intermediate products have so far not been isolated. The known⁹⁰ superior reactivity of the *S*-halogen would suggest the primary formation of *N*-(trichloromethanesulphenyl)amidine (68).

The use of isothiourreas (67; R = S-alkyl) similarly affords 3-alkylthio-5-chloro-1,2,4-thiadiazoles (69; R = S-alkyl) in 35–65% yields.^{89, 91} The method is widely applicable and has provided a variety of 5-chloro-1,2,4-thiadiazoles.^{92–94}

⁸⁸ J. Goerdeler, H. Groschopp, and U. Sommerlad, *Chem. Ber.* **90**, 182 (1957).

⁸⁹ J. Goerdeler, H. Groschopp, U. Schmidt, and G. Sperling, German Patent 960,281 (1957); *Chem. Abstr.* **53**, 8166 (1959).

⁹⁰ J. M. Connolly and G. M. Dyson, *J. Chem. Soc.* 679 (1935); C. S. Argyll and G. M. Dyson, *ibid.* 1629 (1937).

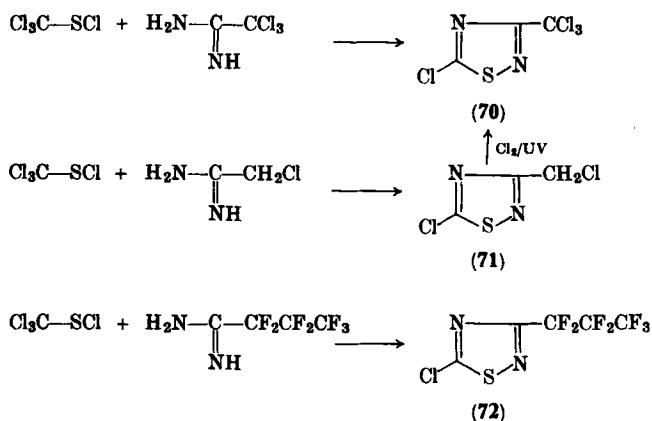
⁹¹ J. Goerdeler and G. Sperling, *Chem. Ber.* **90**, 892 (1957).

⁹² U. Wörffel and R. Behnisch, *Arch. Pharm.* **295**, 811 (1962).

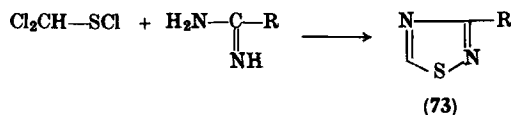
⁹³ U. Wörffel, R. Behnisch, and F. Mietzsch, German Patent 1,079,061 (1960); *Chem. Abstr.* **55**, 27378 (1961).

⁹⁴ J. H. Uhlenbroek and J. D. Bijloo, German Patent 1,132,379 (1962); *Chem. Abstr.* **58**, 892 (1963); J. H. Uhlenbroek and J. D. Bijloo, Netherlands Patent 98,964 (1961); *Chem. Abstr.* **59**, 14001 (1963).

5-Chloro-3-chloro(and trichloro)methyl-1,2,4-thiadiazoles (**71**, **70**) have been obtained from monochloro- and trichloro-acetamidine by this method,⁹⁵⁻⁹⁷ as has the highly fluorinated thiadiazole **72** (from heptafluorobutyroamidine).⁹⁶



b. *Dichloromethanesulfonyl Chloride*, $\text{Cl}_2\text{CH}-\text{SCl}$. In a further modification of this synthesis, the use of dichloromethanesulfonyl chloride⁹⁸ provides directly 1,2,4-thiadiazoles unsubstituted in position 5. 3-Methyl(and phenyl)- (**73**; $\text{R} = \text{Me}$, Ph) and a number of 3-alkylthio-1,2,4-thiadiazoles (**73**; $\text{R} = \text{S-alkyl}$) have been prepared⁹⁹ from amidines and isothioureas, respectively; the reaction proceeds at low temperatures in near-neutral stirred two-phase systems in approximately 45-60% yield.



⁹⁵ U. Wörfel and P. E. Frohberger, British Patent 916,285 (1963); *Chem. Abstr.* **59**, 636 (1963).

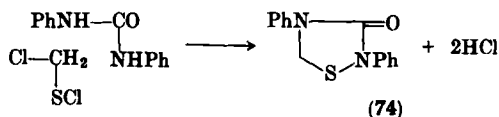
⁹⁶ H. Schroeder, R. F. W. Rätz, W. Schnabel, H. Ulrich, E. Kober, and C. Grundmann, *J. Org. Chem.* **27**, 2589 (1962).

⁹⁷ H. Schroeder and J. H. Reinhart, Belgian Patent 624,636 (1963); *Chem. Abstr.* **59**, 11508 (1963).

⁹⁸ S. R. Wood, U.S., Patent 2,484,061 (1949); *Chem. Abstr.* **44**, 4923 (1950); I. B. Douglas and F. T. Martin, *J. Org. Chem.* **15**, 795 (1950); I. B. Douglas, F. T. Martin, and R. Addor, *ibid.* **16**, 1297 (1951).

⁹⁹ J. Goerdeler and M. Budnowski, *Chem. Ber.* **94**, 1682 (1961).

c. *Monochloromethanesulphenyl Chloride*, $\text{ClCH}_2\text{—SCl}$. Monochloromethanesulphenyl chloride, the lowest member in the series of halogenated methylthiols, reacts with *s*-diphenylurea in boiling chloroform to produce 2,4-diphenyl-3-oxo-1,2,4-thiadiazolidine (74) in 25% yield.¹⁰⁰ *s*-Diphenylthiourea, however, yields only a resinous product of the composition $(\text{C}_{14}\text{H}_{12}\text{N}_2\text{S}_2)_x$.¹⁰⁰



The above general syntheses are obviously capable of wide extension; formamidine and dichloromethanesulphenyl chloride, for example, should yield the parent base directly in one stage.

C. TYPE C SYNTHESSES



The intramolecular interaction of amino and mercapto groups suitably placed in unsaturated organic structures provides well-known general routes to heterocyclic systems. Amongst them, the oxidative cyclization of compounds incorporating the amidinothiono group $[\text{—C(=NH)NH—CS—}]$ has become the basis of a versatile synthesis of 1,2,4-thiadiazoles. The reaction is notable for its speed and the absence of side-reactions: it affords high yields of the desired heterocycles and often provides a clear insight into the structure of the compounds thus formed. The accumulated evidence indicates that 1,2,4-thiadiazoles are generally produced in preference to benzothiazoles, triazoles, or disulfides whenever a choice is open, although such compounds may at times also be formed.

1. 3,5-Disubstituted 1,2,4-Thiadiazole Homologs

N-Thioacylamidines (78), the starting materials required in this synthesis, are most readily accessible by the condensation of nitriles (75) and thioamides (76) in ethereal solution in the presence of hydrogen chloride. This reaction, first performed by Matsui¹⁰¹ and correctly

¹⁰⁰ H. Brintzinger and H. Schmahl, *Chem. Ber.* **87**, 314 (1954).

¹⁰¹ M. Matsui, *Mem. Coll. Sci., Kyoto Univ.* **2**, 401 (1909–10).

interpreted and extended by Ishikawa,^{10, 102-104} may give anomalous results when components (75 and 76) with non-identical radicals are employed. 3,5-Disubstituted 1,2,4-thiadiazoles (79) are often directly formed as by-products and probably arise by air oxidation.

This condensation has been reinvestigated by Peak¹⁰⁵ and more recently in detail by Goerdeler and Porrmann.¹⁰⁶ An excess of hydrogen chloride is desirable in the condensation of aromatic members, but an equimolecular quantity gives optimum results with aliphatic analogs. A number of "mixed" *N*-thioacylamidines were also obtained, though in lower yields.¹⁰⁶ Certain substituted arylthioamides (e.g. 76; R = *p*-MeC₆H₄) are unsuitable because of their immediate precipitation as hydrochlorides.¹⁰⁵

The initial step of this condensation appears to be the attack of the primarily formed imidochloride R—C(:NH)Cl (or [R—C≡NH⁺]Cl⁻) at the sulfur of the thioamide. The resulting diimido-sulfide (77) then rearranges irreversibly to the more stable end-product (78), presumably via an intermediate cyclic stage.¹⁰⁶

A number of related reactions yielding thioacylamidines (78) are of minor preparative importance. They include treatment of thioamides in ether with sulfur monochloride, sulfuryl chloride,^{10, 12} or ozone^{7, 16}; the action of hydrogen sulfide on nitriles in ether containing hydrogen chloride; and the action of hydrogen chloride on ethereal solutions of equimolar quantities of benzonitrile and thioacetic or thiobenzoic acids or certain of their amides.^{107, 108} A limited number of *N*-thioacylamidines (78) have been obtained by the action of hydrogen sulfide-triethylamine on imido-yl-imidochlorides (80) in chloroform.¹⁰⁵

Mild oxidation by bromine,¹⁰¹ iodine,^{10, 28, 103} or nitric acid¹⁰¹ cyclizes *N*-thioacylamidines (78) to 3,5-disubstituted 1,2,4-thiadiazoles (79).^{10, 101, 103} The synthesis has recently been extended to aliphatic members (79; R = alkyl or aryl) which are thus made available in 70-85% yield.²⁸

3,5-Diphenyl-1,2,4-thiadiazole arises by the same general mecha-

¹⁰² S. Ishikawa, *J. Chem. Soc. Japan* **42**, 579 (1921); *Chem. Abstr.* **16**, 1588 (1922); S. Ishikawa, *J. Chem. Soc. Japan* **44**, 382 (1923); *Chem. Abstr.* **17**, 3022 (1923).

¹⁰³ S. Ishikawa, *Sci. Papers Inst. Phys. Chem. Res. (Tokyo)* **7**, 277 (1928).

¹⁰⁴ S. Ishikawa, *Sci. Papers Inst. Phys. Chem. Res. (Tokyo)* **7**, 301 (1928).

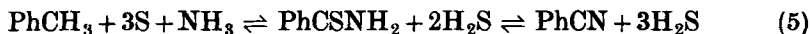
¹⁰⁵ D. A. Peak, *J. Chem. Soc.* 215 (1952).

¹⁰⁶ J. Goerdeler and H. Porrmann, *Chem. Ber.* **94**, 2856 (1961).

¹⁰⁷ S. Ishikawa, *Sci. Papers Inst. Phys. Chem. Res. (Tokyo)* **7**, 293, 295, 298 (1928).

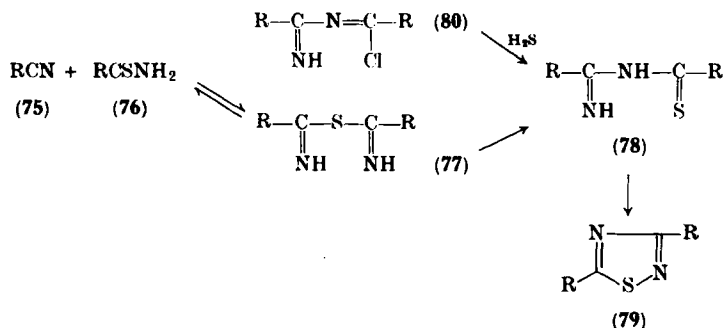
¹⁰⁸ S. Ishikawa, *Mem. Coll. Sci. Kyoto Univ.* **10A**, 191, 196 (1927).

nism when benzonitrile, hydrogen sulfide, and sulfur are heated at 190–215° under pressure. Conversion of part of the nitrile into the thioamide furnishes the components necessary for the formation of the intermediate (78), which then cyclizes under the oxidative influence of the sulfur. In the absence of hydrogen sulfide, the reaction does not occur.¹⁰⁹ The interaction of toluene with sulfur in anhydrous ammonia in closed systems yields thioamides and nitriles reversibly:



Depending on the conditions, the heterocyclic compound 79 may thus be formed as a minor by-product.¹⁰⁹

3,5-Diphenyl-1,2,4-thiadiazole results in small quantities, together with 2,4,6-triphenyltriazine and other products, from the action of alcoholic ammonia and mercuric oxide, or mercuriammonium chloride, or lead hydroxide on *N*-thiobenzoylbenzamidine (78; R = Ph),¹⁰⁵ and from the treatment of the mercuric chloride-adduct of this substituted amidine (78; R = Ph) with potassium hydroxide¹⁰⁴ (probably by air oxidation).



2. 3,5-Diamino-1,2,4-thiadiazoles

a. *From Amidinothioureas.* The oxidative cyclization of the readily accessible amidinothioureas is a general route to variously substituted 3,5-diamino-1,2,4-thiadiazoles. Bromine or hydrogen peroxide in acid media are the most suitable oxidizing reagents, but others have occasionally been used.

Treatment of amidinothiourea (82) with acidified hydrogen peroxide affords the parent compound (83) in excellent yield.¹¹⁰ At higher

¹⁰⁹ W. G. Toland, *J. Org. Chem.* **27**, 869 (1962).

¹¹⁰ F. Kurzer, *J. Chem. Soc.* 1 (1955).

temperatures, however, 30% hydrogen peroxide desulfurizes the starting material to amidinourea (85).¹¹¹ With iodine, the reaction is reversible and fails to go to completion except in very dilute solution.^{56,110,111}

(i) *Structure.* The interpretation of the oxidation and structure of the resulting 3,5-diamino-1,2,4-thiadiazoles is based on the following considerations. Disulfide formation (cf. 84) is ruled out by the observed halogen uptake,^{56,110} molecular weight,^{56,110} and the stability of the products;¹¹⁰ dithioformamidines (84) are known to exist as salts only. The rates of ethanolysis of *N*-pyrazolylamidinothiureas and their hypothetical disulfides should be of the same order, but the oxidation products (i.e. 5-amino-3-(1'-pyrazolyl)-1,2,4-thiadiazoles) are found to solvolyze 30 times more slowly.^{112,113}

The participation of the thiol group in the cyclization is clearly essential, since reaction is prevented when the sulfur is blocked¹¹⁰ (e.g. in amidino-*S*-ethylthiurea). The possible alternative ring closure involving both imino groups in amidinothiurea is ruled out: authentic 3-amino-5-mercapto-1,2,4-triazole (86) is not identical with the oxidation product. Moreover, diguanide and amidinourea, which contain imino groups situated as in amidinothiurea, fail to react with hydrogen peroxide.¹¹⁰ Finally, the possible production of substituted 2-aminobenzthiazoles (92), the usual products of the oxidation by halogens of arylthiureas,¹¹⁴ is rejected on the basis of the non-identity⁵⁶ of the oxidation product of *N*-amidino-*N'*-phenylthiurea (89; R = Ph, R' = H) with the known 2-guanidinobenzthiazole (92).

(ii) *Homologs of 3,5-diamino-1,2,4-thiadiazoles.* The reaction has been extended with success to the preparation of 5-alkyl(or aryl)amino-3-amino-1,2,4-thiadiazoles (90; R = alkyl or aryl; R' = H) from *N*-alkyl (or aryl)-*N'*-amidinothiureas^{56,111} (89; R = alkyl or aryl; R' = H).

3,5-Di(alkyl or aryl)amino-1,2,4-thiadiazoles (90; R,R' = alkyl or aryl) are similarly obtainable in 60–85% yields from the appropriate disubstituted amidinothiureas (89; R,R' = alkyl or aryl).^{56,57} The preparation of the latter from monosubstituted guanidines (87) and isothiocyanate esters (88) might conceivably yield the isomeric ami-

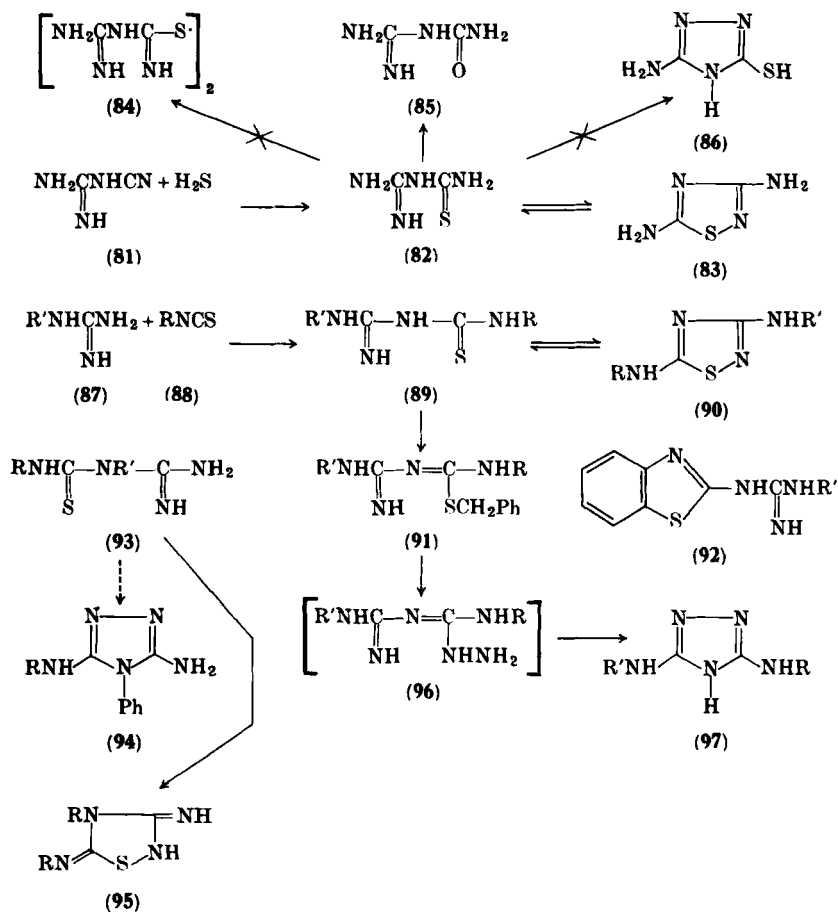
¹¹¹ F. Kurzer, *J. Chem. Soc.* 2288 (1955).

¹¹² F. L. Scott, *Chem. Ind. (London)* 463 (1958).

¹¹³ F. L. Scott, *Chimia (Aarau)* 11, 163 (1957).

¹¹⁴ J. M. Sprague and A. H. Land, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 5, pp. 511, 581. Wiley, New York, 1957.

dinothiureas (**93**), whence 4-aryl-5-arylimino-3-imino-1,2,4-thiadiazolidines (**95**) would be formed on oxidation. However, the correctness of their formulation as **89** is confirmed by the successive *S*-benzylation

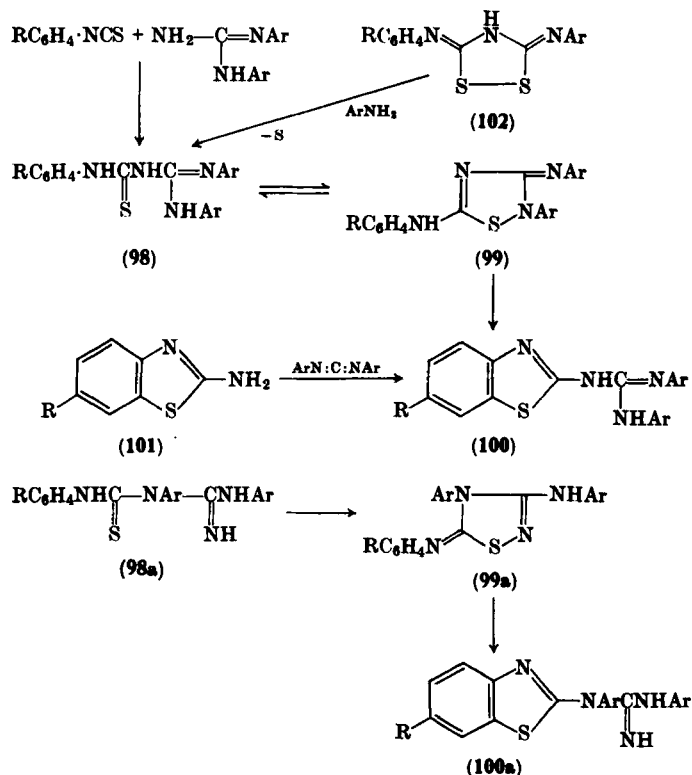


(to give **91**), hydrazinolysis, and cyclization of *N*-phenyl-*N'*-phenyl-amidinothiurea to the known 3,5-dianilino-1,2,4-triazole (**97**; $\text{R} = \text{R}' = \text{Ph}$). By the same reaction sequence, the isomeric amidinothiurea **93** would yield 3-amino-5-anilino-4-phenyl-1,2,4-triazole (**94**).⁵⁷ Further evidence for the preferential attack of isothiocyanate esters at an amino rather than at an anilino group in guanidines is

provided by the results of their reaction with *s*-diphenylguanidine (see page 145).¹¹⁵

Amongst oxidizing reagents, arylsulfonyl chlorides in pyridine simultaneously cyclize and acylate amidinothiourea (and its *N*-phenyl and *N,N'*-diphenylhomologs), producing moderate yields of sulfonyl derivatives of 3,5-diamino-1,2,4-thiadiazoles in one step.¹¹⁶

Monosubstituted amino groups (e.g. anilino) in amidinothioureas can participate in this cyclization, as shown by the ready oxidation of 1-(*N,N'*-diphenylamidino)-3-phenylthiourea (**98**; R = H, Ar = Ph) (and its analogs) to 5-anilino-2-phenyl-3-phenylimino- Δ^4 -1,2,4-thiadiazoline (**99**; R = H, Ar = Ph).¹¹⁶ This reaction, in which the alternative cyclization to benzothiazoles might be expected to predominate,⁵⁸



¹¹⁵ F. Kurzer and P. M. Sanderson, *J. Chem. Soc.* 3240 (1960).

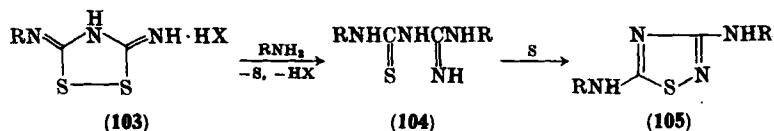
¹¹⁶ F. Kurzer, *J. Chem. Soc.* 2999 (1957).

illustrates the great ease with which the 1,2,4-thiadiazole system is formed. 1,2,4-Thiadiazolines (**99**) thus synthesized^{115, 117} are stable as their salts: the free bases, however, isomerize irreversibly to the corresponding 2-guanidinobenzothiazoles (**100**).¹¹⁵

The trisubstituted amidinothioureas (**98**) required as precursors of the thiadiazolines are obtained by the interaction of isothiocyanate esters and *s*-diarylguanidines,¹¹⁵ or by the action of aromatic amines on dithiazolidines (**102**).¹¹⁷ The former reaction might conceivably yield the isomeric amidinothioureas (**98a**) instead; if so, however, oxidation and isomerization would give rise to a 2-(diphenylguanidino)benzthiazole (**100a**) isomeric with, but different from, the product (**100**) actually obtained. The structure of this product is confirmed by synthesis from 2-aminobenzthiazole (**101**) and carbodiimides.¹¹⁵

The oxidative cyclization of amidinothioureas has been utilized in the preparation of further examples of 1,2,4-thiadiazole derivatives.^{38, 112, 113, 118-122}

(iii) *1,2,4-Thiadiazoles from thiurets.* The action of aromatic^{63, 119-121} (but not aliphatic¹²³) amines on the appropriate diimino-1,2,4-dithiazolidine hydrohalides (**103**) ("thiurets," obtained by the oxidation of dithiobiurets) is an alternative route to amidinothioureas (**104**), which, following the general method, have been oxidized by iodine to homologs of 3,5-diamino-1,2,4-thiadiazoles (**105**).¹¹⁹⁻¹²¹ The sulfur liberated in the first stage tends to oxidize the amidinothiourea as it is



formed, so that the thiadiazole may become a by-product, or indeed the only product, of the initial stage.^{63, 120} The effectiveness of elementary sulfur as an oxidizing reagent in this cyclization has been separately established.¹²⁰

The structure of a considerable number of alleged substituted amidinothioureas and their acetyl derivatives obtained by the above

¹¹⁷ S. N. Dixit, *J. Indian Chem. Soc.* **40**, 365 (1963).

¹¹⁸ F. L. Scott and J. Reilly, *J. Am. Chem. Soc.* **74**, 4562 (1952).

¹¹⁹ K. S. Suresh, *J. Indian Chem. Soc.* **37**, 25 (1960).

¹²⁰ S. N. Dixit, *J. Indian Chem. Soc.* **37**, 151 (1960).

¹²¹ S. N. Dixit, *J. Indian Chem. Soc.* **38**, 221 (1961).

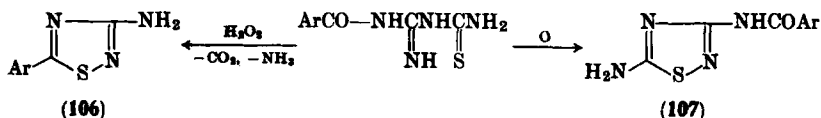
¹²² F. Kurzer and S. A. Taylor, *J. Chem. Soc.* 4191 (1962).

¹²³ S. N. Dixit, *J. Indian Chem. Soc.* **39**, 263 (1962).

reaction by Fromm and his co-workers¹²⁴ must therefore be revised in the light of these findings.

b. *From N-(Aroylamidino)- and N-(Arylsulfonamidino)-thioureas.* Acidified hydrogen peroxide oxidizes *N*-(aroylamidino)thioureas to 5-amino-3-aroylamino-1,2,4-thiadiazoles (107),¹²⁵ thus providing a route to the 3-monoacyl derivatives that are not otherwise accessible, since acylation of 3,5-diamino-1,2,4-thiadiazole yields di- and tri-substituted products directly.¹¹¹

In neutral solution, however, the hydrogen peroxide oxidation proceeds differently, causing evolution of carbon dioxide and eventual formation of 3-amino-5-aryl-1,2,4-thiadiazoles (106),¹²⁵ the structure of which is confirmed by their unequivocal synthesis¹²⁶ from thiobenzoylguanidine (see Section II, C, 2, c). In spite of its being necessarily a multi-stage process,¹²⁵ the reaction proceeds remarkably smoothly and in good yields. The information so far available has not established its mechanism, but it is tempting to postulate the intermediate formation of a thiobenzoylguanidino-type structure, from which the 1,2,4-thiadiazole would arise in the usual way.¹²⁵



N-(Arylsulfonamidino)thioureas (108) afford the expected 5-amino-3-sulfonamido-1,2,4-thiadiazoles (109). The cyclization occurs almost quantitatively under the influence of bromine, but fails with hydrogen peroxide, which cleaves part of the starting material to sulfonylguanidine (110), and desulfurizes part to sulfonamidinourea (111).¹¹⁶

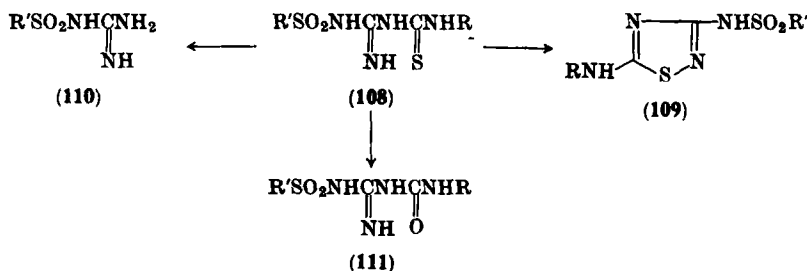
Arylsulfonyl chlorides, which are known to oxidize a variety of thioamides,¹²⁷ also cyclize *N*-(sulfonamidino)thioureas directly to sulfonyl derivatives of amino-1,2,4-thiadiazoles.¹¹⁶

¹²⁴ E. Fromm and K. Schneider, *Ann. Chem.* **348**, 174 (1906); E. Fromm and E. Vetter, *ibid.* **356**, 178 (1907); E. Fromm and H. Baumhauer, *ibid.* **361**, 319 (1908); E. Fromm, R. Heyder, A. Jung, and M. Sturm, *ibid.* **394**, 258 (1912).

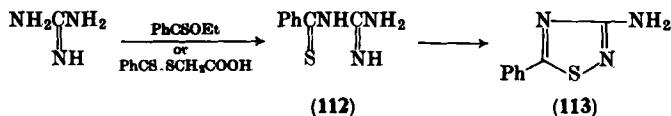
¹²⁵ F. Kurzer, *J. Chem. Soc.* 4524 (1956).

¹²⁶ J. Goerdeler and A. Fincke, *Chem. Ber.* **89**, 1033 (1956).

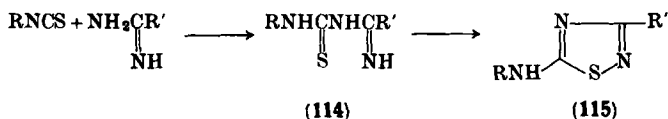
¹²⁷ F. Kurzer, *Chem. Rev.* **50**, 1, 15 (1952).



c. *3-Amino-5-substituted- and 5-Amino-3-substituted-1,2,4-thiadiazoles*. The successive thiobenzoylation and oxidation of guanidine affords the expected 3-amino-5-phenyl-1,2,4-thiadiazole, albeit in low yield. The main losses occur in the first stage, the intermediate thiobenzoylguanidine (112) being too unstable to be isolated in the pure state. Thus, the interaction of guanidine and ethyl thiobenzoate, followed by immediate oxidation, affords the thiadiazole 113 in 25–30% yield.¹²⁶ Only traces of this compound are isolated, however, when thiobenzoylthioglycolic acid is the thioacylating reagent.¹²⁸



5-Alkyl(or aryl)amino-3-substituted-1,2,4-thiadiazoles (115) are synthesized¹²⁹ without difficulty from *N*-substituted-*N'*-acetimidoyl-(or benzimidoyl)thioureas (114), obtained by condensing amidines and isothiocyanates.



3. 3-Hydroxy- and 3-Mercapto-1,2,4-thiadiazoles.

Suitable monothioibiurets are convertible into 3-hydroxy-1,2,4-thiadiazoles by the general reaction as expected. Thus, 4-alkyl-1-aryl-(or alkyl)-2-thioisobiurets (116) are smoothly dehydrogenated, by bromine or acidified hydrogen peroxide, to 3-alkoxy-5-aryl(or alkyl)-

¹²⁸ A. Lawson and C. E. Searle, *J. Chem. Soc.* 1556 (1957).

¹²⁹ F. Kurzer and W. Tertuik, *J. Chem. Soc.* 2851 (1959).

amino-1,2,4-thiadiazoles (**117**), while 1-substituted 2-thiobiurets (**118**) afford the parent 3-hydroxy-1,2,4-thiadiazoles (**119**).¹³⁰ 4-Alkyl-1-methyl-2-thioisobiuret hydrochlorides (**116**; R = Me; Alk = Me, Et) need to be freshly prepared because they tend to rearrange, even in the solid state, to the *S*-alkyl isomers (**121**; R = Me; Alk = Me, Et).¹³¹ 1-Phenyl-2-thiobiuret (**118**; R = Ph), which decomposes in acidic hydrogen peroxide, is cyclized in alkaline medium, which appears to stabilize both the acidic reactant and the product.¹³⁰

By taking advantage of the well-known conversion of the cyano into the carbamoyl group under the influence of alkaline hydrogen peroxide, *N*-aryl-*N'*-cyanoisothioureas (**120**) (as their stable sodio derivatives) are directly cyclizable, in approximately 50% yield, to 5-arylamino-3-hydroxy-1,2,4-thiadiazoles (**119**) in one stage.¹³⁰

The reaction has been extended to the synthesis of the analogous 3-alkylthio heterocycles (**123**) from the appropriate dithiobiurets (**122**).¹³² 1-Substituted 2,4-dithiobiurets (**125**), unlike their monothio-biuret analogs (**118**), are unsuitable as precursors of 1,2,4-thiadiazoles, since in any oxidation the two thiol groups may be expected to react preferentially, resulting in the formation of cyclic disulfides (**126**). The formulation of such oxidation products as 1,2,4-thiadiazoles has indeed been discussed by Bambas¹; however, the available evidence¹³³ favors the cyclic disulfide structure.¹³⁴

If one of the thiol groups in the dithiobiurets is blocked, the cyclization should take the desired course.¹³² Of the two isomeric series of *S*-monosubstituted dithiobiurets, **122** and **127**, the former contains the unsubstituted amidinothiono system and is readily cyclodehydrogenated: Thus, 1-substituted *S*⁴-alkyl(or aryl)iso-2,4-dithiobiurets (**122**) give homologs of 5-amino-3-mercapto-1,2,4-thiadiazole (**123**) in 75–95% yields, preferably by the use of acidic hydrogen peroxide.¹³² Halogens give the same products in somewhat lower yields¹³²; in concentrated solution, however, they tend to cause *S*-debenzylation (to **125**) and subsequent formation of dithiazolidines (**126**).¹³⁵

¹³⁰ F. Kurzer and S. A. Taylor, *J. Chem. Soc.* 379 (1958); F. Kurzer, *Chem. Ind. (London)* 1482 (1956).

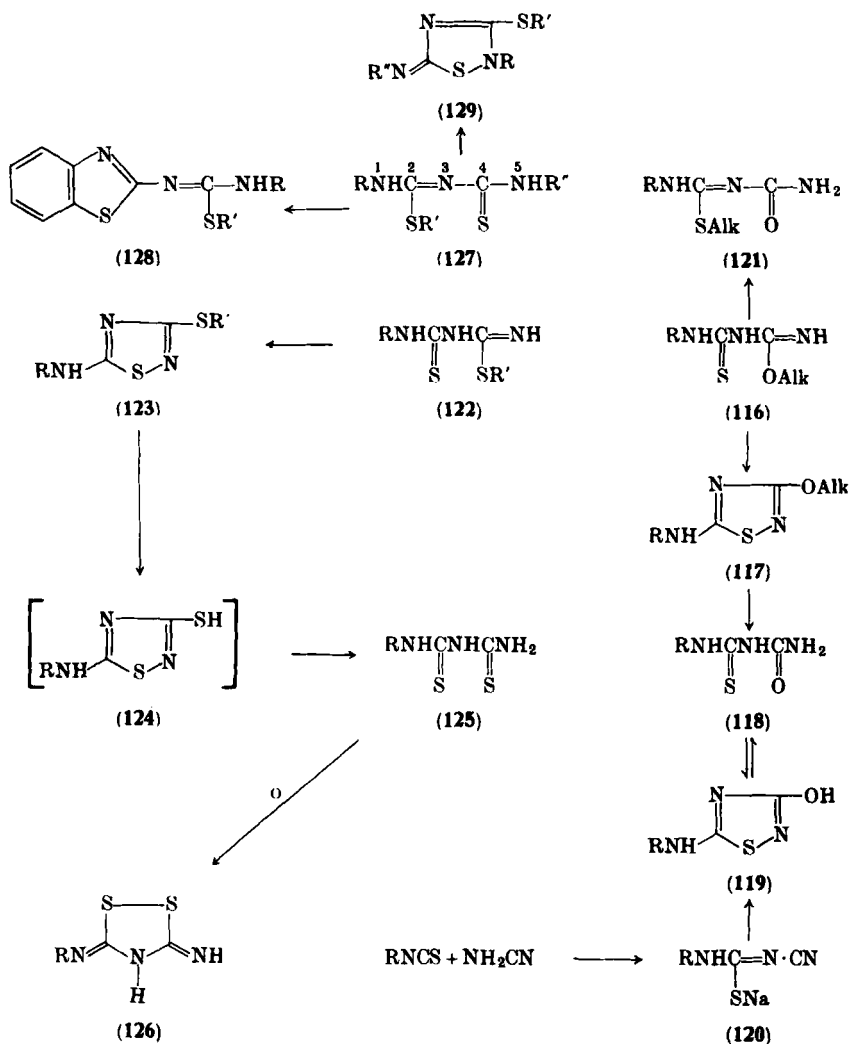
¹³¹ F. Kurzer and S. A. Taylor, *J. Chem. Soc.* 470 (1960).

¹³² F. Kurzer and S. A. Taylor, *J. Chem. Soc.* 1064 (1959).

¹³³ E. Fromm, *Ann. Chem.* **275**, 20 (1893) and subsequent papers; P. W. Preisler and M. M. Bateman, *J. Am. Chem. Soc.* **69**, 2632 (1947); P. W. Preisler, *ibid.* **71**, 2849 (1949).

¹³⁴ F. Kurzer, *Chem. Rev.* **56**, 95, 154 (1956).

¹³⁵ C. P. Joshua and V. K. Verma, *J. Indian Chem. Soc.* **38**, 988 (1961).

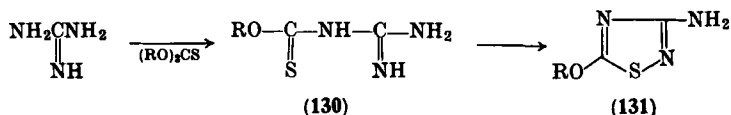


Oxidative cyclization of the isomeric 1-substituted S^2 -alkyliso-2,4-dithiobiurets (127) must involve the participation of a substituted amino group in the ring formation and may therefore be expected to occur less readily.¹³² This is confirmed by the observation¹³⁶ that oxidation of 1,5-diaryl- S^2 -ethylisodithiobiurets (127; $\text{R} = \text{R}' = \text{aryl}$;

¹³⁶ C. P. Joshua, *J. Indian Chem. Soc.* **38**, 155 (1961).

$R' = \text{Et}$) yields, by the familiar Hugershoff cyclization,¹¹⁴ the substituted benzthiazole **128** and not the thiadiazolidine **129**. In 1,5-dialkyl- S^2 -alkylisodithiobiurets (**127**; $R, R', R'' = \text{alkyl}$), which lack an aryl group suitable for benzthiazole formation, oxidation by iodine or bromine causes mainly S -dealkylation and subsequent formation of cyclic disulfides (**126**)¹³⁷; in two cases, however, the formation of thiadiazolines (**129**; $R' = \text{PhCH}_2$, $R = \text{Me}$, $R'' = \text{Me}$ or Et ; and $R' = \text{CH}_2=\text{CHCH}_2$, $R = p\text{-C}_6\text{H}_4\text{Me}$, $R'' = \text{Me}$)^{137,138} as additional products in undisclosed yields, has been observed.

Guanidine cannot be thioacylated by O -alkylchlorothioformates ($\text{RO}-\text{CS}-\text{Cl}$); the action of dialkylthiocarbonates $[(\text{RO})_2\text{CS}]$, however, yields unstable intermediates (**130**) which are cyclized by bromine to 5-alkoxy-3-amino-1,2,4-thiadiazoles (**131**) in low yield (14.5% when $R = \text{Et}$).⁹²



4. 5-Substituted 3-Hydrazino-1,2,4-thiadiazoles

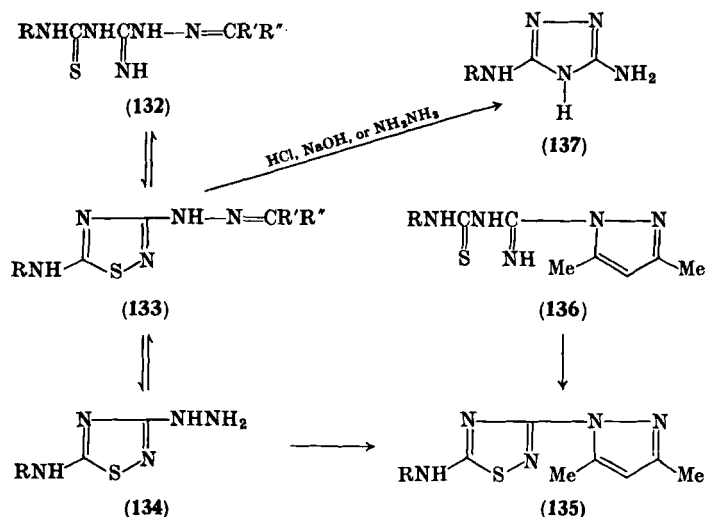
1-Substituted 3-(aminoamidino)thioureas, in the form of their hydrazones (**132**), are readily prepared from isothiocyanate esters and aminoguanidine.¹³⁹ They are exceptionally sensitive towards mineral acids, yielding 3-amino-5-mercapto-1,2,4-triazole,¹³⁹ and cannot, therefore, be oxidized to 1,2,4-thiadiazoles by acidified hydrogen peroxide. Bromine in chloroform, however, effects the desired cyclization readily under carefully controlled conditions: the resulting 1,2,4-thiadiazol-3-yl hydrazones (**133**) are convertible into the hydrazines (**134**) in good yields.¹⁴⁰ Their structure, supported by the usual arguments¹⁴⁰ (see Section II, C, 2, *a*), is further confirmed by the conversion of 5-anilino-3-hydrazino-1,2,4-thiadiazole, by means of acetylacetone, into the pyrazolyl derivative **135**, which is identical with the product obtained by cyclizing 1-[N -(anilinothioformyl)-amidino]-3,5-dimethylpyrazole (**136**).^{112, 113, 118}

¹³⁷ S. N. Dixit, *J. Indian Chem. Soc.* **40**, 153 (1963).

¹³⁸ V. K. Verma, *Indian J. Chem.* **1**, 300 (1963).

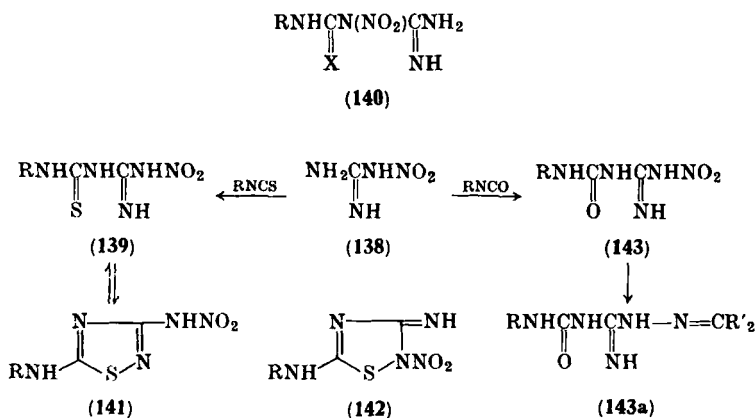
¹³⁹ L. E. A. Godfrey and F. Kurzer, *J. Chem. Soc.* 3437 (1960).

¹⁴⁰ L. E. A. Godfrey and F. Kurzer, *J. Chem. Soc.* 4558 (1963).



5. 5-Substituted 3-Nitroamino-1,2,4-thiadiazoles.

N-Aryl-*N'*-(nitroamidino)thioureas (**139**), obtained from isothiocyanate esters and nitroguanidine (**138**), are cyclizable to 5-arylamino-3-nitroamino-1,2,4-thiadiazoles (**141**) by hydrogen peroxide in the presence of one equivalent of alkali.¹⁴¹ The alternative possible formulation of the starting materials as the 1-amidino-3-aryl-1-nitro isomers



¹⁴¹ L. E. A. Godfrey and F. Kurzer, *J. Chem. Soc.* 4566 (1963).

(140; X = S) is excluded on the basis of the reduction of the corresponding ureas (143) to the known 3-aryl-1-(isopropylideneamino-amidino)ureas (143a; R = Ph). In the absence of rearrangement, the condensation products of isocyanates and nitroguanidine may thus be formulated as nitramines (143), and, by analogy, their sulfur analogs as 139.¹⁴¹

Ring closure of *N*-aryl-*N'*-nitroamidinothioureas (139) at the nitroamino group instead of at the imino group would yield 1,2,4-thiadiazolines of structure 142. The preferred formulation 141 is based on their observed acidity, and on the results¹⁴¹ of the Franchimont color test for distinguishing nitroamines and nitroimines.¹⁴²

D. OTHER SYNTHESSES

1. *Synthesis from Thiocyanic Acid (Isoperthiocyanic and Perthiocyanic Acids)*

In the present account, isoperthiocyanic and perthiocyanic acid are formulated as 144 and 147, respectively. The salient facts supporting these structures are briefly discussed in Section III, J, 1.

Wöhler¹⁴³ first described the formation, from concentrated aqueous thiocyanic acid, of a compound, C₂H₂N₂S₃ later named "isoperthiocyanic acid," and now formulated as 3-imino-5-thiono-1,2,4-dithiazolidine (144). Solutions of isoperthiocyanic acid in alkali deposit sulfur; this redissolves presently giving a liquid containing¹⁴⁴⁻¹⁴⁷ the salt of an isomeric acid, later named "perthiocyanic acid," for which the 3,5-dimercapto-1,2,4-thiadiazole structure is now accepted (see Section III, J, 1). This acid, isolated from its barium salt by treatment with mineral acid and ether extraction,^{144, 145} readily reverts to isoperthiocyanic acid,¹⁴⁴ but fairly stable specimens are obtainable under carefully controlled conditions.^{146, 148}

The production of isoperthiocyanic acid (144) from thiocyanic acid has been investigated kinetically at 0° using ether or ethyl chloride as

¹⁴² A. P. N. Franchimont, *Rec. Trav. Chim.* **16**, 213, 226 (1897); A. F. McKay, *Chem. Rev.* **51**, 301 (1952).

¹⁴³ F. Wöhler, *Ann. Physik.* **69**, 271 (1821).

¹⁴⁴ P. Klason, *J. Prakt. Chem.* **38**, 366 (1888).

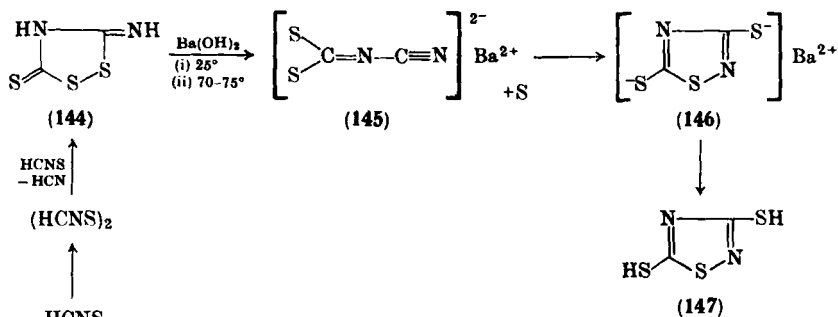
¹⁴⁵ A. Hantzsch and M. Wolvekamp, *Ann. Chem.* **331**, 265 (1904).

¹⁴⁶ E. Söderbäck, *Svensk Kem. Tidskr.* **57**, 62 (1945).

¹⁴⁷ A. Rosenheim, R. Levy, and H. Grünbaum, *Ber.* **42**, 2923 (1909).

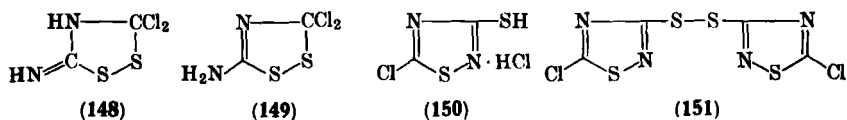
¹⁴⁸ E. Söderbäck, *Acta Chem. Scand.* **1**, 529 (1947).

solvent¹⁴⁹; it probably proceeds by way of a less stable dimeric thiocyanic acid. The isomerization to 3,5-dimercapto-1,2,4-thiadiazole (147) involves an intermediate that has been identified¹⁴⁵ as barium cyanodithiocarbamate (145).

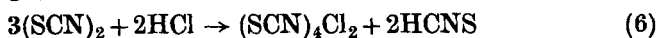


2. Synthesis from Thiocyanogen

The interaction of thiocyanogen and hydrogen chloride in anhydrous ether yields two products of molecular formulae $(\text{SCN})_2 \cdot 2\text{HCl}$ ¹⁵⁰ and $(\text{SCN})_4\text{Cl}_2$,¹⁵¹ respectively. On the basis of its chemical behavior, the first compound was originally formulated¹⁵⁰ as a dithiazolidine (148); a reinterpretation of its formula and reaction in terms of 1,2,4-thiadiazole structures¹ (e.g. 150) appears unwarranted since subsequent X-ray crystallographic measurements,¹⁵² electron density maps,¹⁵³ and infrared spectra¹⁵⁴ have vindicated the original structure, though in its tautomeric form (149). The compound $(\text{SCN})_2 \cdot 2\text{HCl}$ and its transformation products are thus outside the scope of this review.



The second product, $(\text{SCN})_4\text{Cl}_2$,¹⁵¹ which arises from thiocyanogen according to Eq. (6), has been formulated as a di-1,2,4-thiadiazol-3-yl



¹⁴⁹ L. Birckenbach and E. Büchner, *Ber.* **75**, 1771 (1942).

¹⁵⁰ E. Söderbäck, *Ann. Chem.* **419**, 217, 304 (1919).

¹⁵¹ E. Söderbäck, *Ann. Chem.* **465**, 184 (1928).

¹⁵² O. Foss, *Acta Chem. Scand.* **10**, 871 (1956).

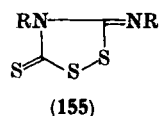
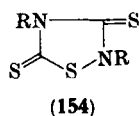
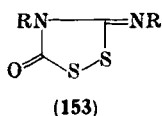
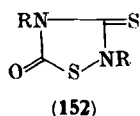
¹⁵³ A. Hordvic, *Acta Chem. Scand.* **14**, 1218 (1960); *ibid.* **15**, 1186 (1961).

¹⁵⁴ H. J. Emeléus, A. Haas, and N. Sheppard, *J. Chem. Soc.* 3165 (1963).

disulfide (151).¹⁵¹ Its infrared spectrum¹⁵⁵ is in agreement with this formulation, though the spectroscopic evidence is less definite than for perthiocyanic acid. With reasonable reservations, the behavior of this compound and its transformation products (see Section III, I) may therefore be interpreted in terms of 1,2,4-thiadiazole structures.¹⁵⁵

3. Syntheses from Isothiocyanates and Dithiocarbamates

Compounds of molecular formulae $(\text{RNCS})_2\text{O}$ and $(\text{RNCS})_2\text{S}$, for which 1,2,4-thiadiazolidine structures have been considered, are obtainable from isothiocyanate esters on oxidation; the latter series is also accessible from dithiocarbamates.



a. *Oxidation of Isothiocyanate Esters.* The isothiocyanate oxides $(\text{RNCS})_2\text{O}$ result from the action of chlorine on ethereal solutions of isothiocyanates, followed by treatment with alkalis¹⁵⁶ or aqueous alcohol,¹⁵⁷ or from the action of bromine on the isothiocyanates in chloroform containing ethanol,^{158,159} or water.¹⁶⁰

Isothiocyanate sulfides, $(\text{RNCS})_2\text{S}$, arise similarly from isothiocyanates by successive treatment with bromine in anhydrous chloroform, and hydrogen sulfide^{158,160} or ethanol.¹⁶¹ The phenyl homolog has also been obtained by the action of thiophosgene on diphenylthiourea,¹⁶² or aluminum chloride on phenyl isothiocyanate.¹⁶³

Freund,¹⁵⁸⁻¹⁶⁰ formulating the "oxides" as substituted 1,2,4-thiadiazolidines (152) and the "sulphides" as 1,2,4-dithiazolidines (155), justified the assignment of unlike hetero-nuclei on the grounds that "sulfides" were also obtainable by the action of bromine on alkyl dithiocarbamates (see below), while "oxides" were unobtainable by the corresponding reaction of alkyl thiocarbamates. Hantzsch and

¹⁵⁵ H. J. Emeléus, A. Haas, and N. Sheppard, *J. Chem. Soc.* 3168 (1963).

¹⁵⁶ E. Sell, *Ber.* 6, 322 (1873).

¹⁵⁷ O. Helmers, *Ber.* 20, 786 (1887).

¹⁵⁸ M. Freund and E. Asbrand, *Ann. Chem.* 285, 166 (1895).

¹⁵⁹ M. Freund and B. Bachrach, *Ann. Chem.* 285, 184 (1895).

¹⁶⁰ M. Freund, *Ann. Chem.* 285, 154 (1895).

¹⁶¹ B. Proskauer and E. Sell, *Ber.* 9, 1262 (1876).

¹⁶² M. Freund and H. Wolf, *Ber.* 25, 1456 (1892).

¹⁶³ A. Friedmann and L. Gattermann, *Ber.* 25, 3525 (1892).

Wolvekamp¹⁴⁵ and Söderbäck¹⁵⁰ later favored dithiazolidine structures (153, 155) and Bambas¹ finally preferred thiadiazolidine structures (152, 154) for *both* classes of compounds.

Bradsher *et al.*¹⁶⁴ have recently based a choice between the thiadiazolidine and cyclic disulfide structures on the presence or absence of an imino group in the molecule, as revealed by a strong absorption in the 6.02–6.21 μ region of their infrared spectra (see also ref. 165). For the isothiocyanate sulfides, this technique vindicates the cyclic disulfide structure (155) in all examples. In isothiocyanate oxides, the nature of the substituents determines the structures: thus, alkyl homologs behave as 1,2,4-thiadiazolidines (152), while the spectra of aralkyl and aryl homologs agree with the cyclic disulfide structures (153).¹⁶⁴

Isothiocyanate oxide hydrobromides,¹⁶⁴ however, all show the characteristic absorption in the imino region; their cyclic disulfide structure (153) is thus indicated, presupposing the isomerization 153 \rightarrow 152 (R = alkyl) on liberation of the free base. When a rearrangement of this type can occur readily, it seems reasonable that the dithiazolidine form (153), incorporating the basic alkylimino group, would be the more stable in the presence of acid.

b. *Isomerization of Isothiocyanate Sulfides.* 4-Methyl-5-methyl-imino-1,2,4-dithiazolidine-3-thione ("methyl isothiocyanate sulfide") (158), but not its homologs,^{160, 164} isomerizes above its melting point, or in alkaline media (e.g. alcohol containing a few drops of ammonia)^{158, 160, 165} or simply on recrystallization from isopropanol¹⁶⁶ to yield a base formulated by Hantzsch and Wolvekamp¹⁴⁵ as 159. Spectroscopic evidence¹⁶⁴ supports this formulation, and incidentally eliminates the 1,2,4-trithiolane structure (160) proposed by Freund¹⁶⁰ (but compare ref. 165). The resulting 1,2,4-thiadiazolidine (159) is reconvertible into 158 by treatment of its salt with cold sodium carbonate solution.¹⁶⁰

The experimental evidence as a whole suggests that both isothiocyanate oxides and sulfides, in the form of their salts, possess the dithiazolidine structures 153 and 155, respectively: the lower alkyl isothiocyanate oxides when liberated rearrange to the 1,2,4-thiadiazolidines (152), but the higher homologs do not. In the isothiocyanate sulfides,

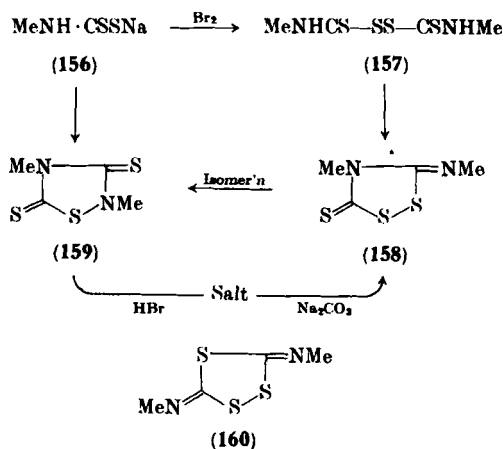
¹⁶⁴ C. K. Bradsher, F. C. Brown, E. F. Sinclair, and S. T. Webster, *J. Am. Chem. Soc.* **80**, 414 (1958).

¹⁶⁵ G. D. Thorn, *Can. J. Chem.* **38**, 2349 (1960).

¹⁶⁶ I. Benghiat, J. B. Bowers, G. E. Lukes, and S. L. Giolito, U.S. Patent 2,863,803 (1958); *Chem. Abstr.* **53**, 6516 (1959).

the cyclic disulfide structure (155) is fairly stable, and only the first member (155; R = Me) has been successfully isomerized to the 1,2,4-thiadiazolidine (154; R = Me). It is therefore suggested that the occurrence of the isomerization, in both oxides and sulfides, is controlled by steric factors.¹⁶⁴

c. *The Oxidation of Dithiocarbamates.* The oxidation by bromine of sodium methyl dithiocarbamate (156)^{158, 160} or dimethylthiuram disulfide (157) yields 4-methyl-5-methylimino-1,2,4-dithiazolidine-3-thione (158), the structural assignment of which by Hantzsch and Wolvekamp¹⁴⁶ is supported by infrared spectroscopic evidence¹⁶⁴ (see also ref. 165).



Isomerization of this cyclic disulfide (see above) affords the 1,2,4-thiadiazolidine (159), also obtainable directly from sodium methyl dithiocarbamate by conveying the wet, finely powdered salt under oxidative conditions through a pneumatic dryer.¹⁶⁶ The production of alkyl (and phenyl) homologs by this procedure is claimed in the patent literature,¹⁶⁶ but no physical constants are given. It is recalled that the isomerization 158 → 159 had previously been thought to be confined to the methyl homologs.^{160, 164}

III. Chemical Properties

A. 1,2,4-THIA DIAZOLE AND HOMOLOGS

The parent compound, first obtained in 1955,⁵ is a volatile liquid, soluble in polar solvents, less so in non-polar ones. Its physical properties are summarized in Table II. Its I.R. spectrum has been recorded.⁵

1,2,4-Thiadiazole forms easily hydrolyzed salts with mineral acids, a methiodide, and 1:1 addition compounds with silver nitrate and mercuric and cobaltous chlorides.⁵ Its weakly basic properties are shared by its homologs^{14, 22} which form salts and adducts similarly.

TABLE II
PHYSICAL PROPERTIES OF 1,2,4-THIADIAZOLE⁵

m.p.	-35 to -33°
b.p. (753 mm)	120.7-121.2°
d_{20}	1.3298
$n_D^{21.2}$	1.5316
Heat of combustion	408 Kcal/mole
λ_{\max}	229 m μ (log ϵ , 3.73)
Polarographic halfwave potential	-2.00 V (water)

Substituents in the 3- and 5-position exert a marked stabilizing influence on the heterocyclic nucleus towards acids, alkalis, and oxidizing and reducing reagents. Thus, the parent compound and its 3-methyl homolog are sensitive to acids (dilute more so than concentrated); the former is rapidly decomposed by cold aqueous alkali to ammonia, hydrogen sulfide, and sulfur.⁵ In contrast, 3,5-diphenyl-1,2,4-thiadiazole resists the action of hot mineral acids,^{8, 9, 101} and prolonged boiling is required for attack by alkalis.⁸ This effect of alkyl and aryl groups on the stability and reactivity in individual series of derivatives is discussed in the relevant sections.

1,2,4-Thiadiazole is easily cleaved by reduction, and is oxidized to sulfate ion by 30% hydrogen peroxide.⁶ Higher homologs require more drastic conditions for reduction^{8, 9, 21, 22} and tend to resist oxidation.

B. HALOGENO-1,2,4-THIADIAZOLES

The strikingly contrasting inertness of the 3-halogeno-thiadiazoles and reactivity of the 5-halogeno-thiadiazoles recalls analogies in the thiazole and pyrimidine series: 2-halogenothiazoles (in which the halogen occupies a position as in 5-chloro-1,2,4-thiadiazoles) are reactive, while the 4- and 5-halogeno isomers are not.⁵⁸ Again, the comparable position of the halogen in 5-chloro-1,2,4-thiadiazoles and 4-chloropyrimidines foreshadows its reactivity towards nucleophilic attack.⁸⁸

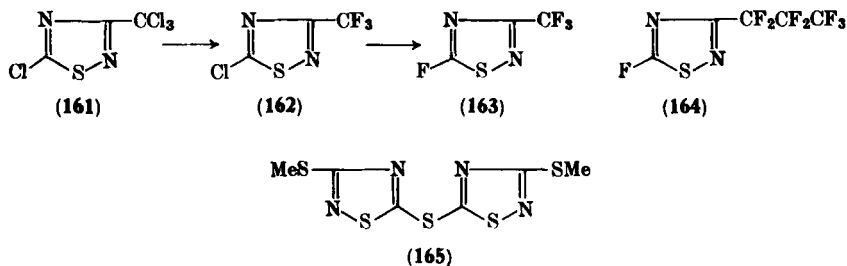
1. 5-Halogeno-1,2,4-thiadiazoles

a. *Physical Properties.* 5-Chloro-1,2,4-thiadiazoles are generally fairly stable,⁸⁸ steam-volatile^{88, 91, 95} liquids or solids with a characteristic odor, sometimes sweetish,^{88, 91} sometimes pyridine-like.⁵

b. *Reduction.* 5-Bromo-1,2,4-thiadiazole⁵ in methanol-triethylamine in the presence of excess of Raney nickel absorbs the calculated amount of hydrogen at ordinary pressure to yield the ultimate parent compound of this series, 1,2,4-thiadiazole, in 72% yield.⁵

5-Halogeno-1,2,4-thiadiazoles are destroyed fairly rapidly by zinc and hydrochloric acid, with evolution of hydrogen sulfide.^{88, 91}

c. *Fluorination.* Silver fluoride, probably the most useful reagent for converting chloro- into fluoro-heterocycles,¹⁶⁷ has been used to prepare 5-fluoro-1,2,4-thiadiazoles,⁹⁶ including the perfluorinated compounds **163** and **164**, from the corresponding 5-chloro derivatives (e.g. **161**) generally in good yields.⁹⁶ Swarts mixture (SbF_3Cl_2) preferentially fluorinates the 3-trichloromethyl group in **161**.⁹⁶



d. *Hydrolysis.* Substituted 5-halogeno-1,2,4-thiadiazoles are hydrolyzed by concentrated sulfuric acid to give the 5-hydroxy compounds.^{88, 91} 5-Hydroxy-1,2,4-thiadiazole, the parent compound, has been obtained by this method.⁵ Sodium alkoxides in the appropriate alcohol,^{88, 96, 97} or alcoholic potassium hydroxide,⁹¹ or sodium phenoxide in acetone¹⁶⁸ convert 5-halogeno-1,2,4-thiadiazoles into the corresponding alkoxides almost quantitatively.

e. *Thiohydrolysis.* The halogen atom in 5-chloro-1,2,4-thiadiazoles may be replaced by a thiol group by the action of thiourea^{88, 91} followed by strong alkali⁸⁸ or ammonia,⁹¹ or by the action of

¹⁶⁷ E. Kober, H. Schroeder, R. F. W. Rätz, H. Ulrich, and C. Grundmann, *J. Org. Chem.* **27**, 2557 (1962) and subsequent papers.

¹⁶⁸ J. Goerdeler and K. H. Heller, *Chem. Ber.* **97**, 225 (1964).

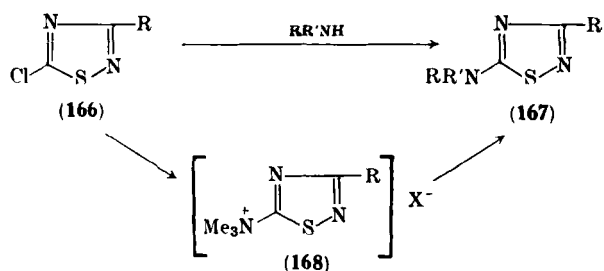
methanolic ammonium sulfide.⁹¹ Isothiuronium salts in alkali similarly effect replacement by arylthiol groups.¹⁶⁹

The action of methylthiol in ammoniacal methanol yields 5-methylthio derivatives⁹¹; the symmetrical bis(3-methylthio-1,2,4-thiadiazol-5-yl)sulfide (**165**) is thus accessible from the appropriate 5-mercapto and 5-chloroheterocycles⁹¹ (see also ref. 168).

The reaction has been further employed to convert 3-alkylthio-5-chloro- into 3,5-di(alkylthio)-1,2,4-thiadiazoles of unequivocal structure: their identity with the di-*S*-alkyl derivatives of perthiocyanic acid has served to establish the structure of the latter⁹¹ (see Section III, J, I).

f. *Aminolysis and Related Reactions.* Aminolysis employing primary and secondary amines^{5, 81, 88, 91, 96, 97, 168, 170, 171} converts 5-chloro-1,2,4-thiadiazoles (**166**) into the corresponding 5-amino derivatives (**167**) rapidly in good yield. Satisfactory results are obtained with aromatic amines which are deactivated by one nitro or cyano group, but 2,4-dinitroaniline, diphenylamine, and 5-amino-1,2,4-thiadiazoles fail to react.¹⁶⁸ Ammonolysis^{91, 97} occurs more slowly and in poorer yields.

Treatment of **166** with excess trimethylamine in benzene yields the quaternary ammonium salts (**168**; R = Ph or SMe); in ethanol,



however, this salt breaks down to the dimethylamino compound (**167**), the excess of trimethylamine probably acting as an acceptor for the eliminated methyl group⁹¹ (see also ref. 168). The observation suggests the potential use of the quaternary salt **168** as an alkylating reagent.⁹¹

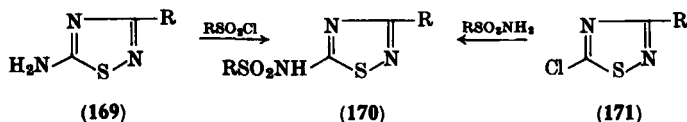
¹⁶⁹ A. Ginsberg and J. Goerdeler, *Chem. Ber.* **94**, 2043 (1961).

¹⁷⁰ J. Goerdeler and K. Deselaers, *Chem. Ber.* **91**, 1025 (1958).

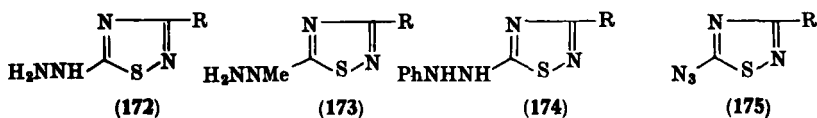
¹⁷¹ J. Goerdeler and W. Roth, *Chem. Ber.* **96**, 534 (1963).

Acetamide replaces a halogen atom (in **166**, R = Ph) by the acetamido group (50–60% yield), while dimethylformamide yields 5-dimethylamino-3-phenyl-1,2,4-thiadiazole quantitatively.¹⁶⁸

The replacement of the reactive 5-chloro by a sulfonamido group in 1,2,4-thiadiazoles affords a convenient synthesis of the 5-sulfonamido heterocycles.^{92, 93, 168, 172, 173} Thus, 5-halogeno compounds (**171**), on treatment with *p*-acetamidobenzenesulfonamide and potassium carbonate in diphenyl ether at 200°, afford the sulfonamido derivatives (**170**) in 70% yields. Nitrobenzenesulfonamides do not react. This route is valuable, because the products are obtainable with difficulty by sulfonylation of the parent amine (see Section III, D, 1, *h*).^{6, 83, 85, 87} The superiority of route **171** → **170** over route **169** → **170**, though unusual in the heterocyclic field, recalls similar observations made in the synthesis of sulfonamidotriazines.¹⁷⁴



g. Hydrazinolysis. Goerdeler and Sperling⁹¹ reported the conversion of a 5-chloro-1,2,4-thiadiazole, by means of excess hydrazine hydrate, into the corresponding 5-hydrazino derivative (**171**; R = SET). Methyl hydrazine gives the 5-(α -methylhydrazino) compound **173**,¹⁷⁰ but phenylhydrazine affords the 5-(ω -phenylhydrazino) derivative **174** (R = SMe).¹⁶⁸ Further examples of this reaction have been provided by Beyer *et al.*¹⁷⁵



¹⁷² U. Wörfel, R. Behnisch, W. Pula, and F. Mietzsch, German Patent 1,069,632 (1959); *Chem. Abstr.* **55**, 16569 (1961); U. Wörfel, R. Behnisch, W. Pula, and F. Mietzsch, British Patent 839,316 (1960); *Chem. Abstr.* **55**, 571 (1961).

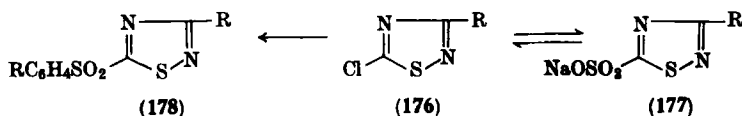
¹⁷³ U. Wörfel, R. Behnisch, and F. Mietzsch, German Patents 1,079,062 and 1,079,063 (1960); *Chem. Abstr.* **55**, 27378–27379 (1961); U. Wörfel, R. Behnisch, and F. Mietzsch, U.S. Patent 2,921,066 (1960); *Chem. Abstr.* **54**, 11054 (1960).

¹⁷⁴ F. Kurzer and J. R. Powell, *J. Chem. Soc.* 2531 (1953); *ibid.* 4152 (1954).

¹⁷⁵ E. Bulka, F. Sommer, and H. Beyer, *Chem. Ber.* **95**, 1983 (1962).

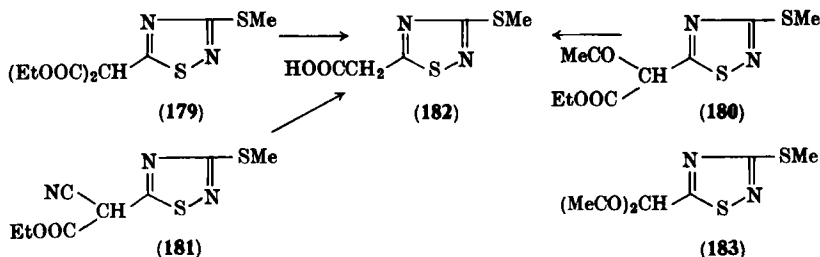
h. *Action of Hydroxylamine and Azide.* The interaction of 5-chloro-3-phenyl-1,2,4-thiadiazole with hydroxylamine in boiling ethanol affords the corresponding 5-hydroxylamino derivative (93% yield).¹⁷⁶ Sodium azide in aqueous acetone provides near-quantitative yields of the 5-azido derivative (175), which is converted by piperidine into 3-phenyl-5-piperidino-1,2,4-thiadiazole.¹⁶⁸

i. *Action of Sulfite and Sulfates.* 3-Substituted 5-chloro-1,2,4-thiadiazoles (**176**; R = Ph, SMe) react with sodium sulfite in aqueous ethanol to yield sodium salts of the corresponding 5-sulfonic acids (**177**); these are reconvertible, on treatment with phosphorus pentachloride, into the starting materials. The action of sodium sulfates similarly produces 60–80% yields of sulfones (**178**) which are somewhat acid and alkali sensitive.¹⁶⁸



j. *Action of Cyanides.* Attempts to exchange the highly reactive 5-chloro group by a cyano group were not successful⁸⁸; prolonged action of cuprous cyanide in boiling dimethylformamide gave merely small yields of the 5-carbonamido derivative.¹⁶⁸

k. *Other Replacements.* Compounds containing reactive methylene groups readily displace the 5-chloro substituent in 1,2,4-thiadiazoles. Thus, 5-chloro-3-methylthio-1,2,4-thiadiazole reacts with malonic, acetoacetic, and cyanoacetic esters (as their sodio derivatives) in benzene to yield products (e.g. **179**, **180**, and **181**) which are deacylated or decarboxylated by 75% sulfuric acid to the corresponding 1,2,4-thiadiazolylacetic acid (**182**).⁹¹ Condensation with acetylacetone occurs more sluggishly, and yields of the product (**183**) are low.⁹¹



¹⁷⁶ J. Goerdeler and K. H. Heller, *Chem. Ber.* **97**, 238 (1964).

The behaviour of 5-halogeno-1,2,4-thiadiazoles in nucleophilic replacement reactions resembles that of 2,4-dinitrochlorobenzene,¹⁷⁷ and has been studied kinetically.¹⁶⁸ The examples selected were second order replacements, involving a rate-determining stage, in which the nucleophilic reagent is added at C-5, followed by rapid elimination of the halogen.¹⁶⁸ The numerical results underline the incomparatively greater difference in reactivity of positions 5 and 3 in 1,2,4-thiadiazoles, compared with that of the 4- and 2-positions in pyrimidine, and may be correlated satisfactorily with Zahradník and Koutecký's⁴ calculations based on the molecular orbital method.

2. 3-Halogeno-1,2,4-thiadiazoles

As has been pointed out, halogen in the 3-position in 1,2,4-thiadiazoles is inert towards most nucleophilic reagents. Thus, under the usual conditions, 3-chloro-5-phenyl-1,2,4-thiadiazole cannot be hydrogenated catalytically to the parent base, and resists aminolysis, hydrazinolysis, and replacement of the halogen by cyano or thiol groups.¹⁷⁸ It is unaffected by concentrated sulfuric acid at 100°, which converts the 5-analogs into the hydroxy compounds.¹⁷⁸

In alkaline media, 3-halogeno compounds appear to be less stable: 3-chloro-5-phenyl-1,2,4-thiadiazole is decomposed completely by 1*M*-alcoholic potassium hydroxide and by hydrazine.¹⁷⁸ Nucleophilic substitution of the 3-halogen atom by alkoxy groups can be achieved, however, by means of sodium alkoxide in the appropriate alcohol: 3-methoxy-, 3-benzyloxy-, and 3-(2'-hydroxyethoxy)-5-phenyl-1,2,4-thiadiazole are obtainable by this route in good yield.¹⁷⁸

C. HYDROXY-1,2,4-THIA DIAZOLES

Hydroxy-1,2,4-thiadiazoles are generally distinctly acidic, stable solids: 3-ethyl-5-hydroxy-1,2,4-thiadiazole, for example, is rather more acidic than nitrophenol and 4-hydroxypyrimidine, but less so than 2,4-dinitrophenol (cf. Table III).⁸⁸

5-Anilino-3-hydroxy-1,2,4-thiadiazole dissolves in dilute alkalis and is reprecipitated by dilute acid; it is, however, appreciably soluble in more concentrated acids (e.g. 3*N*-hydrochloric acid), possibly due to the influence of the basic portion of the heterocyclic nucleus.¹³⁰

¹⁷⁷ W. J. Van Heteren, *Rec. Trav. Chim.* **20**, 107 (1901).

¹⁷⁸ F. Kurzer and S. A. Taylor, *J. Chem. Soc.* 3234 (1960).

3-Hydroxy-5-methylamino-1,2,4-thiadiazole is sufficiently basic to yield a picrate, as are the 3-alkoxy homologs.¹³⁰

3-Hydroxy-1,2,4-thiadiazoles possess phenolic character; they give red to purple colors with ferric chloride, and fail to afford ketonic derivatives.^{130, 178} They resist the action of hot alkaline sodium plumbite.¹³⁰ The 3-alkoxy homologs are neither alkali soluble nor give colors with ferric chloride.¹³⁰

The ultraviolet absorption spectrum¹²² of 5-anilino-3-hydroxy-1,2,4-thiadiazole closely resembles that of the 3-amino analog, for which the 3-enamine configuration seems most likely (see Section

TABLE III
ACIDITY OF 5-HYDROXY-1,2,4-THIADIAZOLE
DERIVATIVES⁸⁸

Compound	pK value
2,4-Dinitrophenol	4.0
3-Methyl-5-mercapto-1,2,4-thiadiazole	5.18
3-Ethyl-5-hydroxy-1,2,4-thiadiazole	6.89
4-Nitrophenol	7.2
4-Hydroxypyrimidine	8.6

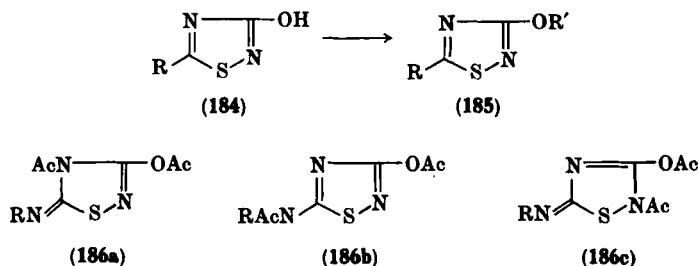
III, D, 1). In spite of this, differences in the spectra of 5-anilino-3-hydroxy- and 3-alkoxy-5-anilino-1,2,4-thiadiazoles suggest that ketonic tautomers of the hydroxy compound contribute to the resultant absorption curve. Similar observations are made with 3-hydroxy-5-phenyl-1,2,4-thiadiazole.¹²² The spectra of 4-methylpyrimid-2-one and 2-methoxy-4-methylpyrimidine led to similar conclusions.¹⁷⁹

Acylation of 3-hydroxy-1,2,4-thiadiazoles (184) by the usual procedures yields monosubstitution products that are formulated as phenolic esters (e.g. 185; R = Ph; R' = Ac, Bz, or *p*-MeC₆H₄SO₂)¹⁷⁸ (see also ref. 130). 5-Anilino-3-hydroxy-1,2,4-thiadiazole affords diacetyl and dibenzoyl derivatives; one acyl residue being assumed to enter the hydroxyl group, the possible structures of the derivatives are 186a-c.¹³⁰

Reduction, by zinc and hydrochloric acid, of 5-anilino-3-hydroxy-1,2,4-thiadiazole causes the usual ring-opening at the S—N bond,

¹⁷⁹ J. R. Marshall and J. Walker, *J. Chem. Soc.* 1004 (1951).

giving good yields of 1-phenyl-2-thiobiuret.¹⁸⁰ Attempts to replace the hydroxyl group by chlorine, by means of phosphorus oxychloride, with or without dimethylamine, were not successful.¹⁷⁸



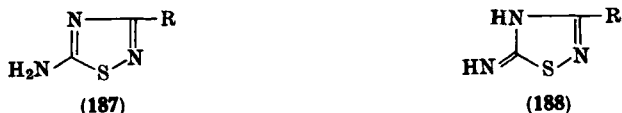
A number of phenolic ethers of this series show the expected properties. 5-Amino-3-ethoxy-1,2,4-thiadiazole is considerably more soluble in water than its 3-methoxy homolog (3.24 and 0.75 g/100 ml, respectively).⁸³ Their ultraviolet spectra resemble those of the 3-alkyl (or aryl)-5-amino-1,2,4-thiadiazoles.⁸³ 3-Alkoxy (or aryloxy)-1,2,4-thiadiazoles are more sensitive towards acids than are the 3-alkyl (or aryl) analogs.⁸³

D. AMINO-1,2,4-THIADIAZOLES

1. 3- and 5-Amino-1,2,4-thiadiazoles

a. *Physical Properties.* 3-Substituted 5-amino-1,2,4-thiadiazoles are generally stable, colorless, odorless compounds.^{6, 83, 85, 129} Their thermal stability (as reflected by their melting points), solubility, and resistance to acids are influenced by the nature of the 3-substituent. 5-Alkoxy-3-amino-1,2,4-thiadiazoles sublime without decomposition.⁸³

Certain physical data, particularly polarographic¹⁸⁰ and spectroscopic evidence⁸¹ (see also ref. 181), suggest strongly that 5-amino-1,2,4-thiadiazoles exist in the enamine (187) rather than the ketimine form (188), but the molecule must assume the latter configuration when



¹⁸⁰ F. von Sturm and W. Hans, *Angew. Chem.* **67**, 743 (1955).

¹⁸¹ A. Shoeb and S. P. Popli, *Indian J. Chem.* **1**, 55 (1963).

substituents are introduced into the appropriate positions. In general, the ultraviolet absorption spectra of the 5-amino compounds (187) show a fairly sharp maximum at 240–245 $m\mu$, while alkylated 5-imino derivatives (188) have a lower, shallower maximum at 230 $m\mu$. The imines are much stronger bases than the amines.

b. *Basicity.* 5-Amino-1,2,4-thiadiazoles (and their 3-alkyl (or aryl)^{6, 79} and 3-alkoxy derivatives⁸³) are weak bases. The basicity decreases on introduction of 3-alkylthio and, more so, of 3-alkylsulfonyl groups.⁸⁶ 3-Amino-1,2,4-thiadiazoles are much weaker bases than the 5-amino analogs (see Table IV). Amino-1,2,4-thiadiazoles form salts with picric,^{6, 81, 125, 129} picrolonic,¹²⁹ and mineral acids,⁶

TABLE IV
BASICITY OF AMINO-1,2,4-THIADIAZOLES¹²⁶

Compound	pK _a value
3-Amino-5-phenyl-1,2,4-thiadiazole	0.1
5-Amino-3-phenyl-1,2,4-thiadiazole	1.4

and may be isolated advantageously as the highly crystalline toluene-*p*-sulfonates.¹²⁹ Picrates derived from 5-amino-3-mercapto-1,2,4-thiadiazoles are decomposed by water.⁸⁵

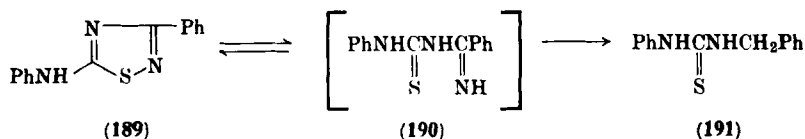
c. *Addition Complexes and Metal Salts.* 5-(and 3)-Amino-1,2,4-thiadiazoles and silver nitrate form difficultly soluble adducts in the molar ratio 1:1.^{6, 87, 126} Silver and mercury salts of 5-anilino-3-phenyl-1,2,4-thiadiazole have been obtained.⁷⁵

d. *Reduction.* In general, reducing reagents preferentially attack amino-1,2,4-thiadiazoles at the N—S bond, causing a cleavage that is comparable with the easy hydrogenolysis of sulfenamides.¹⁸² The resistance of individual compounds to reduction depends largely on the presence of substituents elsewhere in the molecule.

5-Amino-1,2,4-thiadiazoles liberate iodine, though not quantitatively, from potassium iodide in mineral acid solution.⁶ Hydrogen sulfide in acid solution degrades the parent compound completely to thiourea, sulfur, and ammonium chloride, but it is without effect on the acetyl derivative.⁶

¹⁸² M. Busch, *Ber.* 29, 2127 (1896).

Zinc and hydrochloric acid remove the ring sulfur from 5-amino-1,2,4-thiadiazoles as hydrogen sulfide.^{6, 85} 5-Anilino-3-phenyl-1,2,4-thiadiazole (189) is slowly degraded, by the same reagent, to *N*-benzyl-*N'*-phenylthiourea (191),¹²⁹ probably by the usual ring-opening at the N—S bond, followed by the further reductive hydrolysis of the intermediate (190); the latter can indeed be similarly reduced.¹²⁹



The 3-amino isomers are more resistant towards reduction: 3-amino-5-phenyl-1,2,4-thiadiazole is not affected by hydrogen sulfide or acidified potassium iodide, but does undergo decomposition under the influence of stannous chloride in acids or sodium in alcohol.¹²⁶ Zinc in hydrochloric acid cleaves the heterocyclic nucleus completely, benzoic acid and hydrogen sulfide being the main products,¹²⁵ while, under the same conditions, the 3-toluene-*p*-sulfonyl derivative yields benzaldehyde and toluene-*p*-sulfonylguanidine.¹²⁵

e. *Action of Acids.* In general, amino-1,2,4-thiadiazoles are resistant to the action of acids under mild conditions. Prolonged treatment with hot mineral acids, however, may result in their complete decomposition to sulfur and other simple degradation products.⁶ Alcoholic hydrochloric acid decomposes 5-amino-1,2,4-thiadiazole to dithioformamidine $[\text{NH}_2\text{C}(=\text{NH})\text{S}]_2 \cdot 2\text{HX}$, possibly by way of a primary ring-cleavage to an intermediate sulfenic acid derivative.⁶

3-Alkoxy derivatives are attacked more rapidly by 2*N* hydrochloric acid, with liberation of sulfur, than are the 3-alkyl derivatives.⁸³ 3-Alkylthio groups also increase the sensitivity of 5-amino-1,2,4-thiadiazoles to hydrolysis: the 3-phenylthio homolog, for example, tends to decompose on crystallization from boiling water.⁸⁵

f. *Action of Alkalis.* 5-Amino-1,2,4-thiadiazoles are decomposed by hot alkalis, with evolution of ammonia, the sensitivity of the compound depending again on the nature of the substituent in position 3.^{5, 6, 85} 5-Alkyl(or aryl)amino-3-phenyl-1,2,4-thiadiazoles are unaffected by boiling alkaline sodium plumbite, but the 3-methyl analogs deposit lead sulfide slowly.¹²⁹

3-Amino-5-phenyl-1,2,4-thiadiazole is very stable towards hydrolysis, being cleaved only very slowly by boiling concentrated sodium hydroxide, or hydrochloric acid.^{125, 126}

g. *Alkylation*. The results of the methylation⁸¹ of 5-amino-1,2,4-thiadiazoles (**192**; R = H, Ph) are summarized in the reaction scheme: the preferential substitution at N(4) is noteworthy. The resulting hydroiodides are converted into the free bases by silver oxide-methanol.^{171, 183} The formulation of the monomethyl derivative as **193** follows from its unequivocal synthesis from *N*-methylamidine⁸¹; from its degradation reactions (see reaction scheme), when the *N*-methylated thiourea grouping is preserved in each case (thus excluding the possibility of 2-methylation in **192**); and from spectroscopic⁸¹ and polarographic evidence.¹⁸⁰

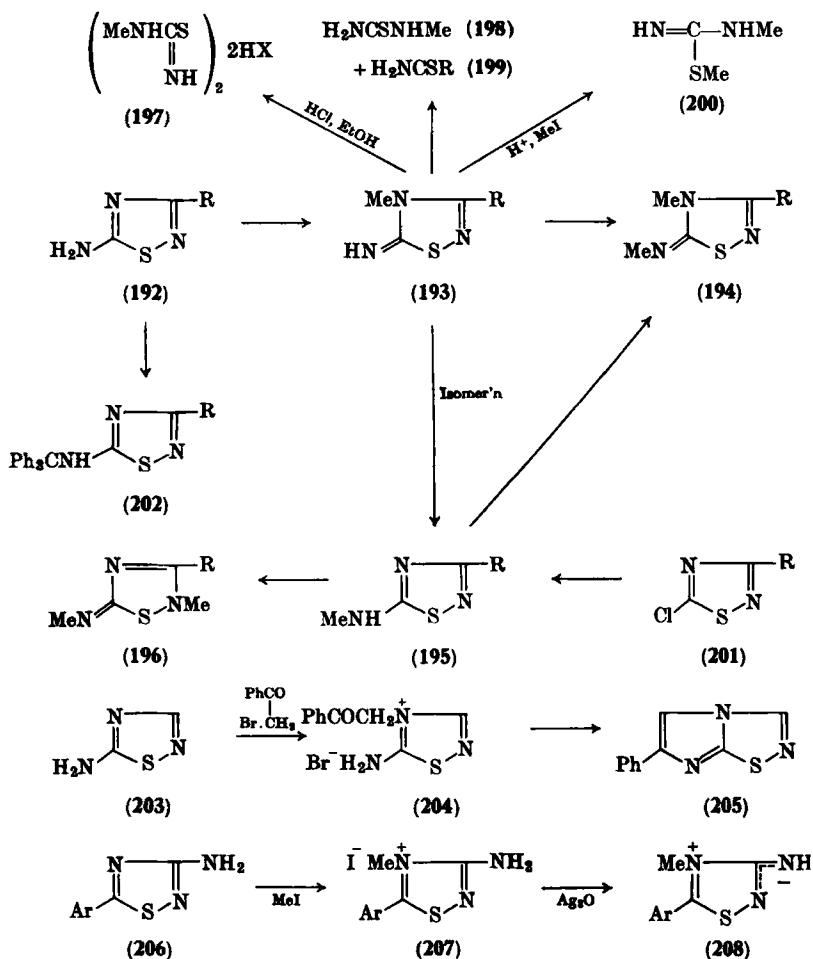
The corresponding ethylation proceeds in lower yields, and may be suppressed entirely by the presence of substituents elsewhere in the nucleus (e.g. **192**; R = Ph).¹⁷¹ The attempted introduction of higher alkyl, allyl, and benzyl residues also failed.¹⁷¹ The derivative (**204**) obtained with phenacyl bromide is readily ring-closed to the diheterocycle **205**.¹⁷¹ Diphenyl- and triphenyl-methyl halides, on the other hand, alkylate 5-amino-1,2,4-thiadiazoles in the exocyclic amino group,¹⁷¹ as shown by the lower basicity of the resulting products (e.g. **202**).

5-Methylamino-1,2,4-thiadiazole (**195**) (but not its 3-phenyl homolog) arises irreversibly¹⁷¹ by isomerization of 5-imino-4-methyl-1,2,4-thiadiazoline (**193**) in ethanol on prolonged storage or brief heating.^{81, 171} The structure is confirmed by its alternative synthesis from **201**.⁵ Further methylation (of **195**) (to **194**, and **194** + **196** when R = Ph) follows the general scheme.⁸¹

A careful re-examination of the isomerization **193** → **195**¹⁷¹ has established its wider applicability (provided that R = H) as well as its mechanism. Model experiments with the comparable methylated 2-aminopyrimidine (having its amino group labelled with ¹⁵N) suggest that the isomerization proceeds by a "flipping-over" process; this involves ring-cleavage at C(3)—N(4), rotation of the RN and HN= groups about the S—C(5) bond, followed by the incorporation of the originally exocyclic imino group in the newly formed ring. The decrease in energy content in passing from the imino to the aromatic amino structure determines the direction and irreversibility of this change.¹⁷¹

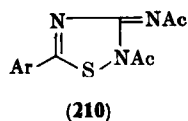
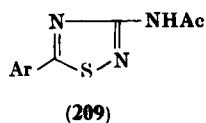
Methylation of 3-amino-5-phenyl-1,2,4-thiadiazole (**206**) proceeds remarkably slowly, yielding products of a zwitter-ion character; the reaction has therefore been interpreted by the sequence **206** → **207** → **208**.¹⁷¹

¹⁸³ B. Helferich and W. Klein, *Ann. Chem.* **450**, 225 (1926).



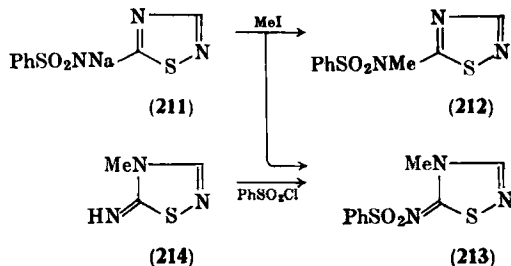
h. *Acylation.* 5-Amino-1,2,4-thiadiazoles⁶ (including 3-phenyl,¹²⁹ 3-dialkylamino,⁸⁷ 3-alkoxy,⁸³ 3-alkylthio,⁸⁵ and 4-methyl derivatives⁸¹) are convertible into alkali-soluble monoacylated products, formulated as 5-acylamino(or imino) derivatives. (See also refs. 74 and 129). 3-Alkylsulfonyl-5-amino-1,2,4-thiadiazoles, being distinctly acidic, do not readily react with acetic anhydride at 100°; acylation does take place, however, in alkaline media.⁸⁶ 3-Amino-5-phenyl-1,2,4-thiadiazole yields mono-^{125, 126} and di-acyl derivatives,¹²⁵ formulated^{122, 125} as 209 and 210, respectively.

In general, acylation of the amino group increases the stability of the resulting 1,2,4-thiadiazole towards acid and alkaline hydrolysis^{6,85}



i. *Sulfonyl Derivatives.* Contrary to a claim in the parent literature,¹⁸⁴ 5-amino-1,2,4-thiadiazoles do not react smoothly with sulfonyl chlorides, and yields of the 5-sulfonamido derivatives tend to be low.^{6, 81, 83, 85, 87, 92, 172, 185} The more reactive 3-alkylsulfonyl-5-amino-1,2,4-thiadiazoles are reported to react more readily.⁸⁶

Proof for the formulation of the resulting derivatives as 5-sulfonamido-1,2,4-thiadiazoles is provided by the series of reactions outlined in the appended scheme.⁸¹ The benzenesulfonyl derivative (211) of 5-amino-1,2,4-thiadiazole yields, on methylation, two monomethylated products (212 and 213). Since the presence of the sulfonyl group (in 213) on the 5-imino group is shown by the alternative synthesis $214 \rightarrow 213$, it follows that the sulfonyl group (in 211) is also attached to the exocyclic 5-amino group.⁸¹

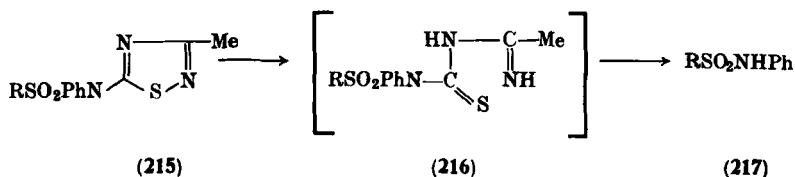


5-Anilino-3-methyl-1,2,4-thiadiazole (but not the 3-phenyl analog) forms a mono-tosyl derivative,¹²⁹ which is degraded to toluene-*p*-sulfonanilide (217) on reductive hydrolysis; this again establishes a 5-sulfonamido structure (215) for the derivative.¹²⁹

3-Amino groups, on the other hand, are sulfonylated with less difficulty,^{125, 126} although here yields may again tend to be unsatisfactory.⁹² The synthesis of the sulfanilamido derivative from 3-amino-1,2,4-thiadiazole is described in the parent literature.¹⁸⁴

¹⁸⁴ J. Laudon, Swedish Patent 115,999 (1946); *Chem. Abstr.* **40**, 7236 (1946).

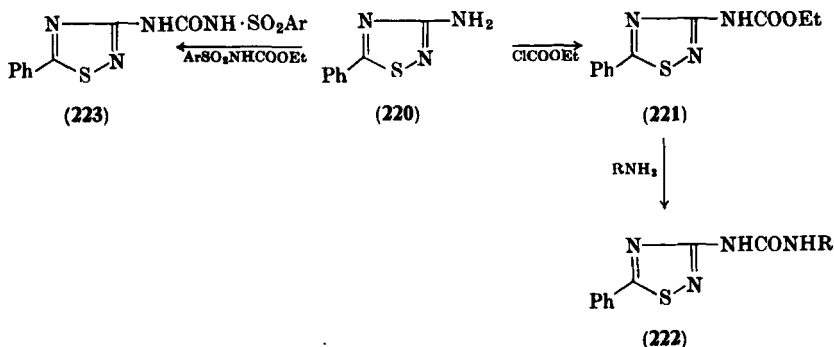
¹⁸⁵ A. Shoeb, S. P. Popli, and M. L. Dhar, *J. Indian Chem. Soc.* **40**, 369 (1963).



j. *Ureido derivatives.* 5-Amino-3-methyl-1,2,4-thiadiazole (218) reacts readily with phenyl isocyanate, yielding the appropriate substituted urea¹⁸⁵ (219); analogous compounds have been similarly prepared.⁸¹



5-Phenyl-3-ureido-1,2,4-thiadiazoles (222) are obtainable by successive treatment of the 3-amino heterocycle (220) with ethyl chloroformate at 120° and the appropriate amine.¹⁸⁵ Direct action of arylsulfonylurethanes (on 220) affords 3-arylsulfonylureido-5-phenyl-1,2,4-thiadiazoles (223) in one stage.¹⁸⁵

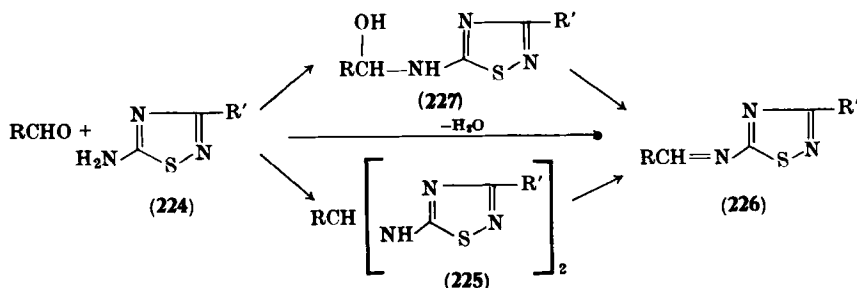


k. *Nitration.* The successful nitration of 5-amino-1,2,4-thiadiazoles has been described. 5-Nitroamino derivatives are obtained on treatment of 5-amino-3-methyl-1,2,4-thiadiazole with concentrated nitric acid in sulfuric acid, or on dissolution of 5-amino-1,2,4-thiadiazolium nitrate in 90% sulfuric acid.¹⁸⁶

l. *Azomethines and Benzylidene-bis-amines.* The condensation of 5-amino-1,2,4-thiadiazoles (224) and aldehydes produces benzylidene-

¹⁸⁶ C. Holstead, Belgian Patent 619,423 (1962); *Chem. Abstr.* 59, 12826 (1963).

bis-amines (**225**); prolonged interaction-in boiling toluene and simultaneous removal of water affords azomethines (**226**). The intermediate α -aminoalcohol (**227**; R = H or Cl_3C) may be isolated when formaldehyde or trichloroacetaldehyde are employed. Azomethines are also accessible from the benzylidene-bis-amines (**225**) on treatment with phenyl isocyanate; the substituted urea formed as a by-product can usually be separated without difficulty.¹⁸⁷

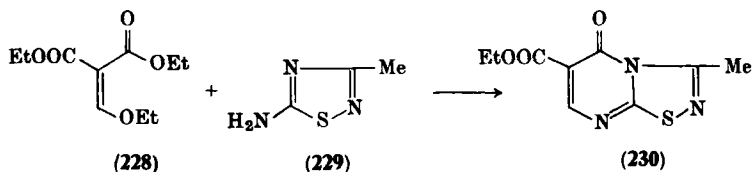


Azomethines are colorless to pale-yellow, low-melting solids, which react with water to form benzylidene-bis-amines [Eq. (7)]. A variety



of addition products (e.g. with ethanol, piperidine, *N*-methylaniline, and *p*-thiocresol) are readily obtainable, and are cleaved into their components by heat.¹⁸⁷

m. *Condensation to a Bicyclic System.* The condensation of 5-amino-3-methyl-1,2,4-thiadiazole (**229**) and diethyl ethoxymethylene-malonate (**228**) in boiling trichlorobenzene yields the bicyclic compound **230** (5-carbethoxy-3-methyl-4-oxo-1-thia-2,3a,7-triazaindene). The location of its keto group in position 4 (rather than in the possible alternative 6-position) is supported by spectroscopic evidence.¹⁸⁸



¹⁸⁷ J. Goerdeler and H. Ruppert, *Chem. Ber.* **96**, 1630 (1963).

¹⁸⁸ C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. Van Allen, *J. Org. Chem.* **24**, 779 (1959).

2. 3,5-Diamino-1,2,4-thiadiazoles

3,5-Diamino-1,2,4-thiadiazole^{110, 111} and its homologs^{56, 111} are weak bases. Their highly crystalline toluene-*p*-sulfonates are particularly suitable for isolation purposes^{110, 111, 115} and their sparingly soluble picrates for identification.^{56, 111, 115} 3-Amino-5-arylamino-1,2,4-thiadiazoles are remarkably soluble in hot caustic alkalis and are deposited unchanged therefrom on cooling.⁵⁶

A comparison of the dissociation constants shows that 5-amino-3-dialkylamino-1,2,4-thiadiazoles are only slightly more basic than the 3-alkyl-5-amino analogs. The low basicity of these compounds suggests that they exist, like the 5-monoamino analogs (see Section III, D, 1), as enamines rather than as the more basic tautomeric ketimines.^{81, 87} The prevalence of the 3-enamine form in 3-amino-5-anilino-1,2,4-thiadiazoles is supported by ultraviolet absorption data.¹²²

a. *Action of Alkalis.* The resistance of 3,5-diamino-1,2,4-thiadiazoles to alkaline reagents depends upon their degree of substitution^{56, 87, 110, 111}; the parent compound is stable to 10% ammonia, pyridine at 100°, or cold alkalis, but is rapidly decomposed by hot alkalis to amidinourea.^{110, 111} The stability of the 5-alkyl (and aryl) amino homologs is considerably higher;^{56, 111} thus, aryl homologs are unaffected after several hours' refluxing in 3*N* sodium hydroxide.⁵⁶

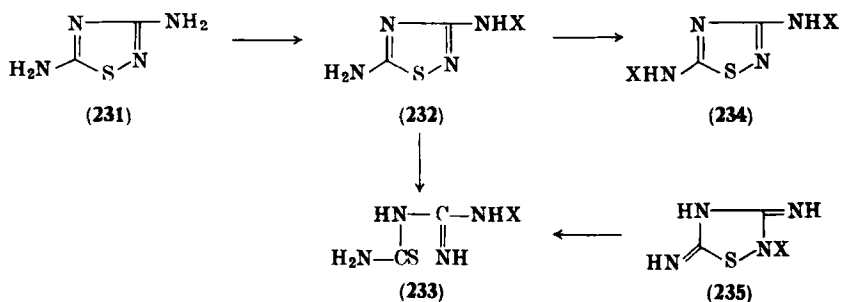
In general, substituted 3,5-diamino-1,2,4-thiadiazoles resist the action of alkaline sodium plumbite,^{56, 111, 125} except the parent compound¹¹⁰ which deposits lead sulfide on brief warming.

b. *Reduction.* 3,5-Diamino-1,2,4-thiadiazoles may be reduced almost quantitatively to the amidinothiureas from which they arise on oxidation (see Section II, C, 2). Their stability towards reducing reagents increases with the degree of substitution of the amino groups. Reduction invariably causes cleavage of the nucleus at the S—N bond, at least as the primary change.

Zinc in hydrochloric acid is sufficiently powerful to open the heterocyclic ring in all cases.^{56, 110} Sulfur dioxide reduces the parent compound rapidly under the mildest conditions, but does not attack homologs or substitution products (e.g. sulfonyl derivatives).¹¹¹ The use of these reagents, and of hydrogen sulfide, in reducing 1,2,4-thiadiazolidines is dealt with in Section II, A, 2.

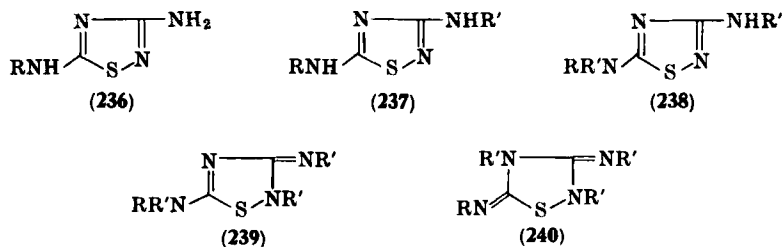
c. *Acylation.* Under appropriate conditions, 3,5-diamino-1,2,4-thiadiazole yields monosulfonyl-, di- and tribenzoyl-, and diacetyl- and dipropionyl derivatives.¹¹¹ The first of these may be assigned the 3-sulfonamido structure (232; X = SO₂C₆H₄CH₃) with some confi-

dence,¹¹¹ since it yields *N*-(toluene-*p*-sulfonamidino)thiourea (**233**; $X = \text{SO}_2\text{C}_6\text{H}_4\text{CH}_3$) on reduction, and is independently obtainable in the direct cyclization of the latter (**233**).¹¹⁶ The alternative possible 2-sulfonamido structure (**235**) is rejected because of the observed acidity of the product, and the analogous known exocyclic acylation of other amino-heterocyclics (e.g. 2-sulfonamidothiazoles¹⁸⁹). On this basis, the 3,5-diacylamido-1,2,4-thiadiazole structure (**234**) is assigned to the diacylated products¹¹¹ and receives support from the alternative



synthesis of the 3,5-diacetamido compound **234** ($X = \text{Ac}$) by the oxidation of acetylthiourea (see Section II, A, 1).²⁷

3-Amino-5-methylamino-1,2,4-thiadiazole similarly gives a 3-toluene-*p*-sulfonamido^{111, 122} (**237**) and a monobenzamido derivative (for structure, see ref. 122); an excess of the appropriate reagent yields non-acidic di- and tri-substitution products, the latter probably of structure **239**. With acetic anhydride, however, acylation terminates with the formation of the 3-monoacyl derivative.^{111, 122} Similar observations are on record concerning 3-amino-5-anilino-1,2,4-thiadiazole⁵⁶; the only anomalous observation is the ability of this compound to form di- and tri-acetyl derivatives.⁵⁶



¹⁸⁹ R. J. Fosbinder and L. A. Walter, *J. Am. Chem. Soc.* **61**, 2032 (1939); W. A. Lott and F. H. Bergheim, *ibid.* **61**, 3593 (1939).

The ultraviolet absorption spectrum¹²² of the diacetyl derivative of 3-amino-5-anilino-1,2,4-thiadiazole is almost identical with that of 3,5-diacetamido-1,2,4-thiadiazole; the former compound may therefore be assigned structure **238** ($R = \text{Ph}$; $R' = \text{Ac}$); the corresponding triacetyl derivative is thus more likely to be **239** ($R = \text{Ph}$; $R' = \text{Ac}$) than **240** ($R = \text{Ph}$; $R' = \text{Ac}$).⁵⁶ A comparison of relevant absorption spectra¹²² suggests further that di- and tri-benzoyl derivatives of 3-amino-5-methylamino-1,2,4-thiadiazole should be represented as **238** ($R = \text{Me}$; $R' = \text{PhCO}$) and **239** ($R = \text{Me}$; $R' = \text{PhCO}$), respectively, and the tribenzoyl derivative of the 5-anilino analog as **239** ($R = \text{Ph}$; $R' = \text{PhCO}$) rather than **240** ($R = \text{Ph}$; $R' = \text{PhCO}$) as had originally been assumed.⁵⁶

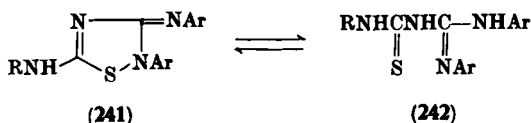
3,5-Diarylamino-1,2,4-thiadiazoles give only mono-acetyl and -benzoyl derivatives, irrespective of the excess of acylating reagent employed, but form a ditoluene-*p*-sulfonyl derivative readily.^{56,57,120} Evidence obtained with 5-anilino-3-phenyl-1,2,4-thiadiazole¹²⁹ suggests that the second sulfonyl group enters the 5-arylamino group in such cases, resulting in the formation of 3,5-di(toluene-*p*-sulfonylanilino) derivatives.

The resemblance between 3-dialkylamino- and 3-alkyl-5-amino-1,2,4-thiadiazoles is again reflected by the fact that both yield mono-acetyl derivatives; attempted sulfonylation fails in the former case and gives low yields in the latter.^{6,87}

It is clearly difficult, from the experimental evidence so far available, to account for the degree of acylation in the individual compounds. Moreover, the site of substitution remains undecided in some cases.^{56,111}

d. *Nitrosation*. 5-Amino-3-dialkyl(or diphenyl)amino-1,2,4-thiadiazoles are not readily diazotized and coupled. Their treatment with sodium nitrite in formic acid has yielded nitrosamines in some cases.⁸⁷

e. *5-Amino-3-imino- Δ^4 -1,2,4-Thiadiazolines and 3,5-Diimino-1,2,4-Thiadiazolidines*. 1,2,4-Thiadiazolines (**241**) are monacid bases, forming somewhat labile salts. They are readily cleaved at the N—S bond by hydrogen sulfide under the mildest conditions to the corresponding amidinothiureas (**242**). Alkaline hydrolysis ruptures the nucleus completely, giving diphenylurea and phenylcyanamide, which arise from the N(2)—C(3) and N(4)—C(5) fragments of the nucleus, respectively. Alkaline sodium plumbite causes rapid desulfurization.¹¹⁵ The ready isomerization of the free bases to 2-(guanidino)benzthiazoles, again necessitating cleavage of the N—S bond, has already been described¹¹⁵ (see Section II, C, 2).

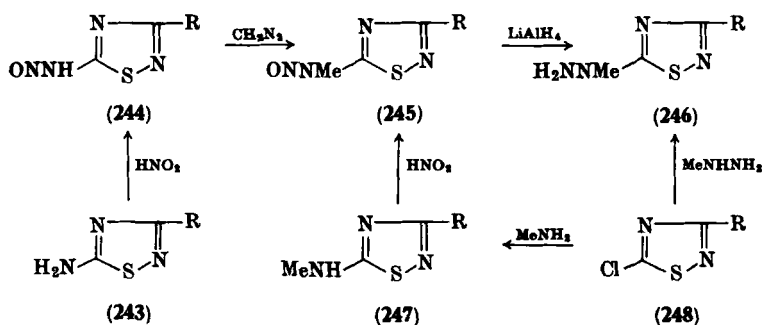


The lower stability of the thiadiazolines than that of the corresponding thiadiazoles is ascribed to the disappearance of the aromatic character of the structure,¹¹⁵ and is well authenticated in the heterocyclic field.³

The properties of 3,5-diimino-1,2,4-thiadiazolidines are discussed in Section II, A, 2.

E. NITROSAMINO-1,2,4-THIA DIAZOLES

Although 3-amino-1,2,4-thiadiazoles (e.g. the 5-phenyl homolog) fail to yield nitrosamines under the usual conditions,¹²⁶ 5-nitrosamines are well known.^{81, 85, 190, 191} Thus, 3-alkoxy-,⁸³ 3-alkylthio-,⁸⁵ 3-dialkylamino-,⁸⁷ and 3-alkylsulfonyl-5-amino-⁸⁶ (243) as well as 3-aryl-5-arylamino-1,2,4-thiadiazoles,⁷⁴ on treatment with the calculated quantity of sodium nitrite in dilute mineral acid, or concentrated formic acid, yield crystalline nitrosamines (244). Their unusual stability has permitted a close study of their formation and properties.¹⁷⁰ Their positive Liebermann reaction^{85, 87, 170} and the results of their methylation (outlined in the reaction scheme) show that nitrosation occurs in the side-chain and not in the nucleus.¹⁷⁰

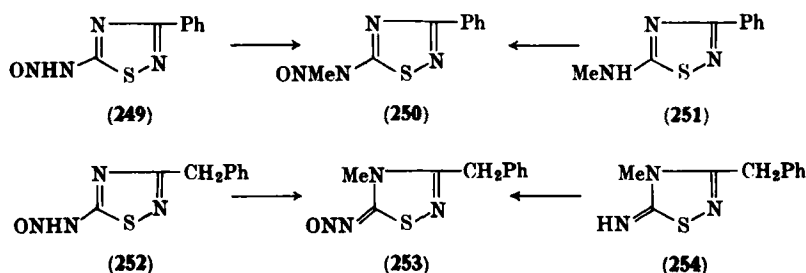


5-Nitrosamines are pale-yellow to orange crystalline solids which decompose vigorously, but not explosively, at their melting points, and are not sensitive to friction and mechanical shock. Like their

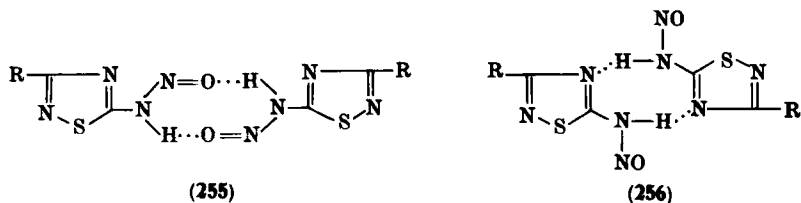
¹⁹⁰ J. Goerdeler, K. Deselaers, and A. Ginsberg, *Chem. Ber.* **93**, 963 (1960).

¹⁹¹ J. Goerdeler, *Angew. Chem.* **65**, 321 (1953).

parent amines, they appear to possess the (nitroso)amino rather than the (nitroso)imino structure, a view that is supported by a comparison of their ultraviolet absorption spectra with those of "fixed" structures.¹⁷⁰ However, methylation with diazomethane may attack the compounds at the nitrosamino group, or at the heterocyclic ring, depending on the nature of the 3-substituent, thus suggesting the existence of the nitrosimino form under suitable conditions. The appended reaction scheme summarizes two well-documented examples: the structures of the methylated products (**250** and **253**) are confirmed, in each case, by an alternative synthesis.¹⁷⁰ No evidence was found for the existence of diazohydroxide forms.

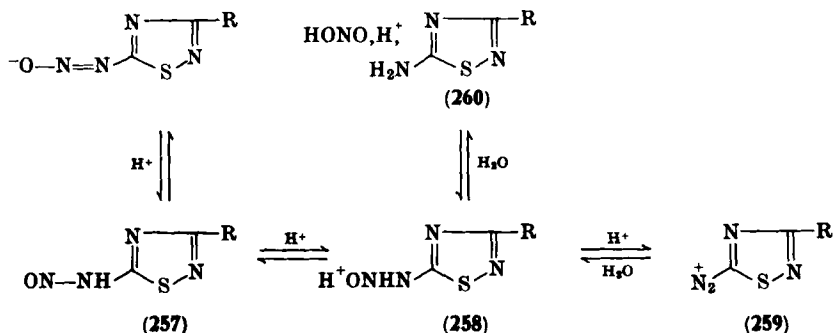


5-Nitrosamines show a strong tendency to associate; molecular weight determinations in non-polar media suggest the existence of dimeric forms, possibly due to the presence of hydrogen bonds in structures such as **255** or **256**.¹⁷⁰



5-Nitrosamines (**257**) are amphoteric; their acidic character is shown by their dissolution in alkalis, producing intensely dark-colored liquids from which the starting material may be regenerated by acids.¹⁷⁰ Due to their weakly basic properties, they also dissolve in strong sulfuric and phosphoric acid and may be extracted therefrom, at least partially, by ether. In these acidic media, equilibrium mixtures are formed with the corresponding diazonium salt which may be precipitated under suitable conditions (see Section III, H, 1). 3-

Alkylsulfonyl-5-nitrosamines have an increased stability-range in acidic media and require acids of high concentration (e.g. 80% sulfuric acid) for their conversion into the diazonium salts.⁸⁶



In strongly acid media, 5-nitrosamines decompose gradually with evolution of nitrogen and nitrous acid fumes, and formation of 5-hydroxyl derivatives in moderate yields. Urea promotes denitrosation to the amine, while the use of hydrohalogen acids yields the corresponding 5-halogeno-1,2,4-thiadiazoles^{170, 190} (see Section III, H, 2, e). Thus, 5-chloro-3-phenyl-1,2,4-thiadiazole is accessible in good yield by the action of methanolic hydrochloric acid on the appropriate nitrosamine.

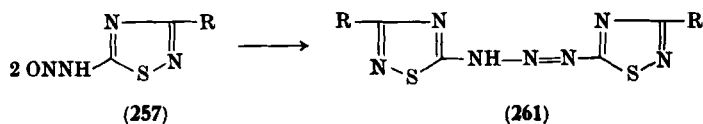
The reduction of nitrosamines to hydrazino compounds is accomplished by lithium aluminum hydride: 5-(α -methylhydrazino)-3-phenyl-1,2,4-thiadiazole has been obtained in 65% yield by this method.¹⁷⁰

In acid media, 5-nitrosamines can couple with suitable phenolic (and other) compounds to yield azo-dyes.^{126, 170} The nitrosamine need not be isolated; the amine is treated, in 50% sulfuric or 85% phosphoric acid, with a slight excess of sodium nitrite, and the resulting solution is immediately used in the coupling process^{80, 170, 192} (see Section III, H, 2, a).

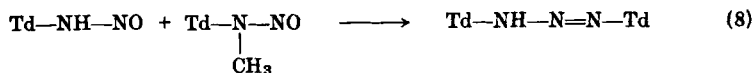
1. Formation and Properties of Triazens (Diazoamino-1,2,4-thiadiazoles)

In aqueous or alcoholic solutions, two molecules of 5-nitrosamine (257) undergo self-condensation to triazens (diazoamino-1,2,4-thiadiazoles) (261).^{86, 170, 191} The reaction is catalyzed by hydrogen ions and

¹⁹² K. Taube, German Patent 927,944 (1955); *Chem. Abstr.* **49**, 12842 (1955); K. Taube, British Patent 760,618 (1956); *Chem. Abstr.* **51**, 9166 (1957); K. Taube, U.S. Patent 2,791,579 (1957); *Chem. Abstr.* **51**, 12497 (1957).



yields of 60–90% may be achieved. In their exhaustive study of this reaction, Goerdeler *et al.*¹⁹⁰ discussed possible mechanisms and examined the influence of changes in reaction conditions on its course. In particular, a study of the formation of “mixed” triazens [e.g. by interactions outlined by Eqs. (8) and (9)] afforded some insight into the nature of these undoubtedly complicated changes.¹⁹⁰



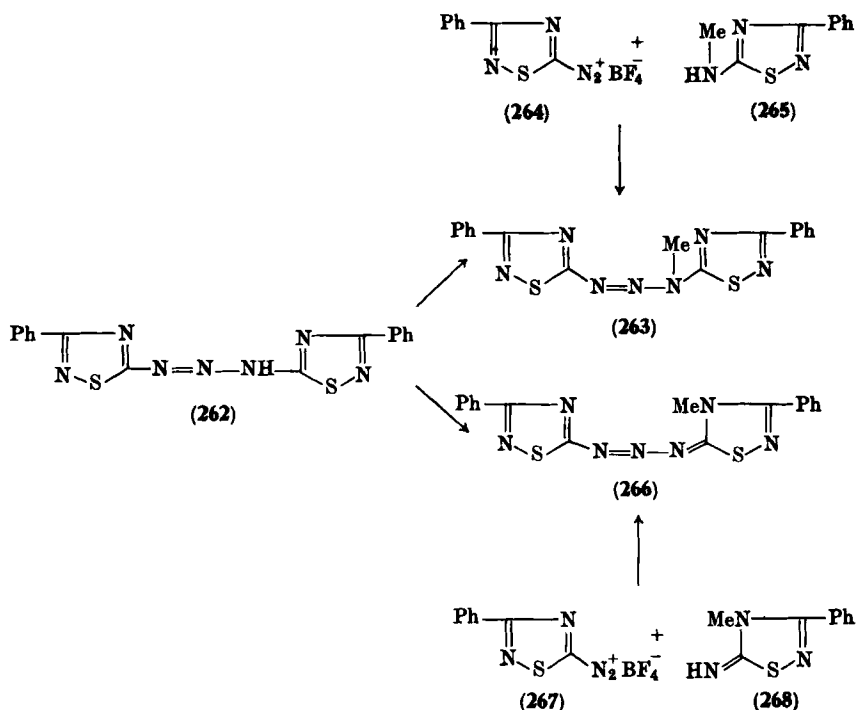
Td = 1,2,4-thiadiazol-5-yl

The diazoamino-thiadiazoles are yellow crystalline solids which decompose vigorously at their melting points.¹⁹⁰ They dissolve in alkalis, and the corresponding alkali salts may be isolated from the resulting deeply colored solutions.¹⁹⁰ They are remarkably resistant towards acids, being split into the 5-amino- and 5-hydroxy-thiadiazoles only on prolonged treatment with 30% sulfuric acid.¹⁹⁰ It is therefore not surprising that triazens cannot be rediazotized and coupled with phenols. It also follows that triazens are not primary products of the diazotization of amino-1,2,4-thiadiazoles.

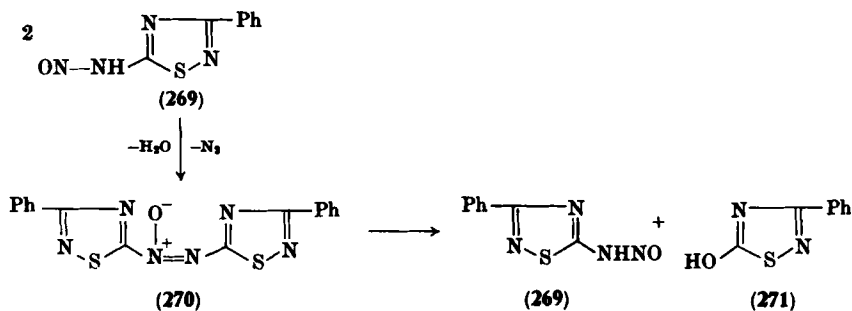
Methylation of the triazen **262** by diazomethane in ether yields **263**, the structure of which follows from its unequivocal synthesis from **264** and **265**.¹⁹⁰ In methanol, minute quantities of the isomer **266** are formed as a by-product (3%); the structure of **266** is similarly confirmed by synthesis from **267** and **268** and supported by spectral data.¹⁹⁰

2. Azoxy-1,2,4-thiadiazoles

The self-condensation of 5-nitrosamino-3-phenyl-1,2,4-thiadiazole (**269**) proceeds differently in benzene, the products being the orange-red azoxy-thiadiazole **270** (40% yield), together with 3,5-diphenyl-

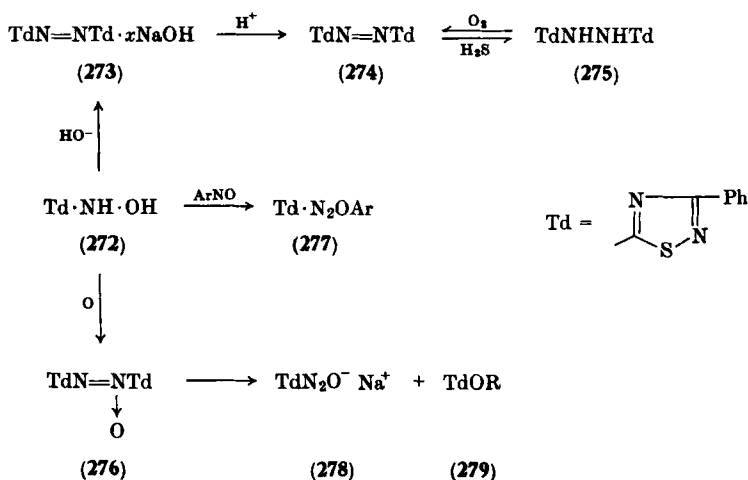


(12%) and 5-hydroxy-3-phenyl-1,2,4-thiadiazole (30% yield). The structure assigned to the azoxy compound (270) is supported by its alkaline degradation to the nitrosamino- (269) and hydroxy-thiadiazole (271) and by its alternative synthesis from the substituted hydroxylamine (272)¹⁹⁰ (see below).



F. HYDROXYLAMINO-1,2,4-THIADIAZOLES

The properties of 5-hydroxylamino-3-phenyl-1,2,4-thiadiazole (**272**) have been studied in some detail.¹⁷⁶ The compound dissolves in alkalis, giving intensely green solutions (**273**), from which the red azo-1,2,4-thiadiazole **274** is precipitated upon acidification. Hydrogen sulfide reduces **274** to the colorless hydrazothiadiazole **275**, which is reconverted, by air oxidation in alkaline solution, into **273** (i.e. **274** as base-adduct).



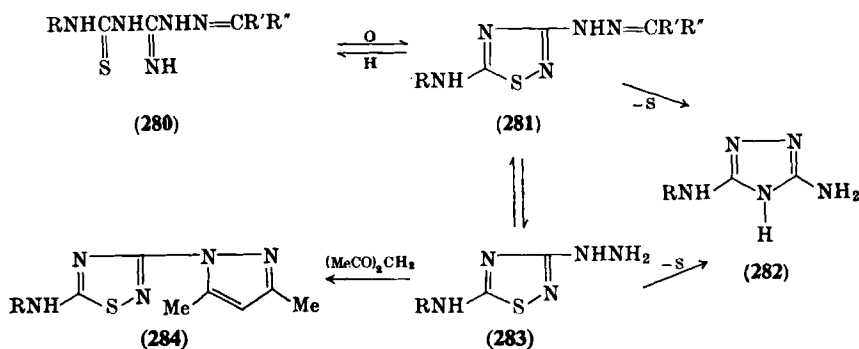
Oxidation, by chromic-acetic acid, of the hydroxylamine **272** yields the azoxy-thiadiazole **276** quantitatively, presumably via a primary nitrosamine: the interaction of the hydroxylamine (**272**) with suitable nitrosamines does indeed afford mixed azoxy-thiadiazoles (**277**), but their exact structure is not known. Alkaline hydrolysis of *s*-azoxy-thiadiazole (**276**) yields the 1,2,4-thiadiazole diazotate **278** and hydroxy(or alkoxy)-1,2,4-thiadiazole **279**, depending on the hydrolytic reagent employed¹⁷⁶ (see also ref. 190).

G. HYDRAZINO-1,2,4-THIADIAZOLES

1. 3-Hydrazino-1,2,4-thiadiazoles

1,2,4-Thiadiazol-3-yl-hydrazines (as their hydrazones) (**281**), obtained from the appropriate amidinothioureas (**280**) on oxidation, are reconverted thereto on mild reduction by sulfur dioxide.¹⁴⁰

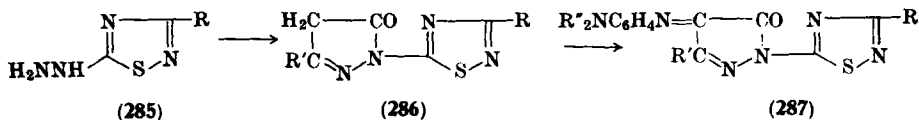
5-Arylamino-3-hydrazino-1,2,4-thiadiazoles (**283**) and their hydrazones (**281**) are readily interconvertible; both are quickly decomposed by acids or alkalis with loss of sulfur, and rearrangement to 3-amino-5-arylamino-1,2,4-triazoles (**282**)¹⁴⁰. In this reaction, the approach of the terminal hydrazino-nitrogen to C(5) would create a spatially favorable situation for the formation of the new five-membered ring (**282**) by simple extrusion of sulfur, requiring no further rearrangement. In the stable 5-hydrazines^{90, 170} this potential configuration is absent.



Treatment of the hydrazine **283** with acetylacetone yields the corresponding 1-substituted 3,5-dimethylpyrazole (**284**); incorporation of the hydrazino group into this new heterocyclic ring has a striking stabilizing effect on the 1,2,4-thiadiazole ring of the resulting compound.¹⁴⁰

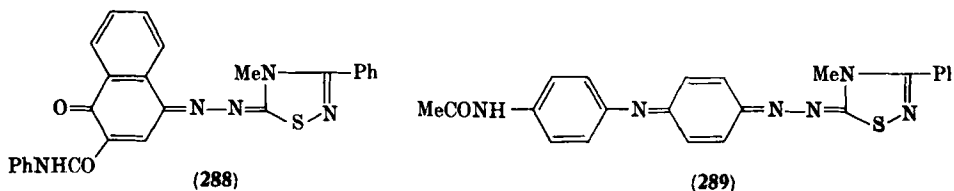
2. 5-Hydrazino-1,2,4-thiadiazoles

5-Hydrazines (of type **285**; R = Me, Ph, or C₆H₄NO₂-*m*) are similarly converted by means of β-keto-esters into 1-(1,2,4-thiadiazol-5-yl)-3-alkylpyrazol-5-ones (**286**), and thence by *p*-nitrosodialkylanilines into the azomethine dyes (**287**), the absorption spectra of which have been recorded.¹⁷⁵

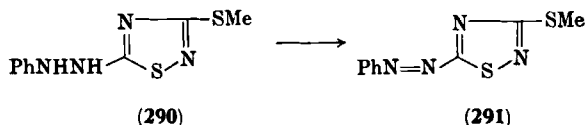


4-Methyl-3-phenyl-1,2,4-thiadiazol-5-one hydrazone contains the amidrazone group necessary for oxidative coupling with suitable phenols or amines to yield azo-dyes. Thus, condensation products (**288**

and **289**) with 1-hydroxynaphthoic-2-anilide and 4-acetamidodiphenylamine are readily obtained, in the presence of potassium ferricyanide and ammonium persulfate, respectively.¹⁹³ The absorption properties of these dyes (**288** and **289**) have been determined and compared with those of related compounds.¹⁹³



Thiadiazolyl-5-hydrazines show the expected reducing action towards ammoniacal silver nitrate, and yield ketonic derivatives.¹⁷⁶ 3-Methylthio-5-(ω -phenylhydrazino)-1,2,4-thiadiazole (**290**) is oxidized by yellow mercuric oxide in ethanol to the azo compound **291**.¹⁶⁸



3. Nitroamino-1,2,4-thiadiazoles

5-Arylamino-3-nitroamino-1,2,4-thiadiazoles are crystalline solids which explode at their melting points. They are monobasic acids, remarkably stable to alkalis and to the action of boiling sodium plumbite. Mild reduction by sulfur dioxide reconverts 5-anilino-3-nitroamino-1,2,4-thiadiazole into its parent amidinothiourea from which it arises by oxidation. Attempts to reduce 3-nitroamino compounds to the corresponding 3-hydrazines were not successful.¹⁴¹

H. 1,2,4-THIADIAZOLE DIAZONIUM SALTS

1. Preparation

The equilibrium existing between nitrosamines and diazonium salts of 1,2,4-thiadiazoles in acid media was mentioned in Section III, E. Diazonium salt solutions may be directly prepared from the amines in concentrated sulfuric, phosphoric, or acetic acid.^{5, 80, 170, 191} Most of

¹⁹³ S. Hünig and K. H. Oette, *Ann. Chem.* **641**, 104 (1961).

the information on record concerns diazonium salts derived from 5-amino-1,2,4-thiadiazoles.

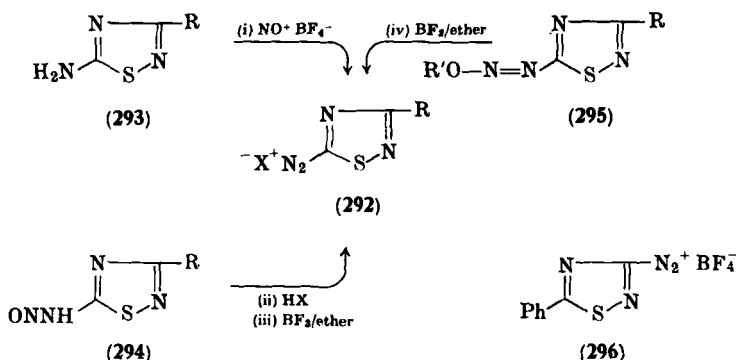
In their detailed study of thiadiazole diazonium salts (292) Goerdeler and his co-workers have succeeded in isolating these compounds in the solid state by the following preparative methods:

(i) Action of nitrosyl tetrafluoroborate (NO^+BF_4^-)¹⁹⁴ on the *amine* (293) in glacial acetic acid at low temperatures.¹⁶⁹ This procedure is particularly valuable when the nitrosamine is not readily available; it is the only method by which a diazonium salt (296) has been obtained from a 3-amino-1,2,4-thiadiazole.¹⁶⁹

(ii) Action of acids (e.g. HBF_4 , HClO_4 , and H_2SO_4) on the *nitrosamine* (294) in glacial acetic acid.¹⁶⁹

(iii) Action of borofluoride etherate in ether on the *nitrosamine* (294).^{86, 169}

(iv) Action of borofluoride etherate in ether on the *diazoether* (295).¹⁶⁹



In each case the diazonium salt is isolated as the sparingly soluble tetraborofluorate (292; $\text{X} = \text{BF}_4$) or perchlorate (292; $\text{X} = \text{ClO}_4$); these form hygroscopic colorless to orange, crystalline solids. The tetrafluoroborates are reasonably stable to shock and friction, but the perchlorates are explosive. Acetone and acetonitrile are useful solvents for studying their reactions in solution.

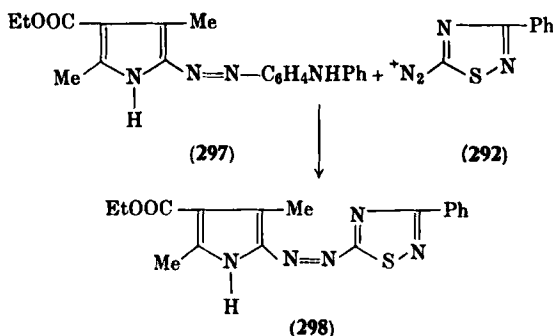
2. Chemical Properties

a. *Coupling Reactions. Formation of Monoazo-Dyes.* Solutions of thiadiazole diazonium salts couple readily with a variety of compounds

¹⁹⁴ G. Balz and E. Mailänder, *Z. Anorg. Allgem. Chem.* **217**, 161 (1934).

(e.g. 2-naphthol, 2-naphthylamine, and phenol), including reagents of inferior coupling power, such as benzene derivatives lacking hydroxyl or amino groups (e.g. 3-chloro-*N,N*-diethylaniline).^{5,83,85,191,192}

In a comparative study of the coupling power of a variety of diazotized heterocyclic amines, Goerdeler *et al.*⁸⁰ demonstrated the high reactivity of 1,2,4-thiadiazoles. 5-Amino-1,2,4-thiadiazoles exceeded in this respect not only a variety of related amino-heterocyclics (thiazoles, benzthiazoles, 1,2,4-triazoles, and tetrazoles), but also 2,4-dinitroaniline: thus, competitive coupling with β -naphthol of a mixture of 2,4-dinitrobenzenediazonium fluoroborate and 3-phenyl-1,2,4-thiadiazol-5-yl diazonium fluoroborate resulted in the exclusive formation of an azo-dye from the latter compound.⁸⁰ 3-Phenyl-1,2,4-thiadiazol-5-yl diazonium salt will actually displace azo groups derived from weaker coupling reagents (e.g. in **297**).¹⁹⁵ The high coupling power of



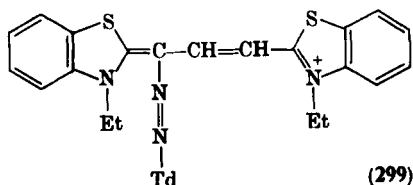
diazonium salts derived from 5-amino-3-alkylsulfonyl-1,2,4-thiadiazoles is illustrated by the good yields of azo-dyes obtainable with *m*-xylene (75%) or phenoxyacetic acid (31%).⁸⁶

These and other experiments show that diazonium salts incorporating the 1,2,4-thiadiazole ring are undoubtedly among the most reactive examples of their kind.⁸⁰ Their reactivity is attributable to the electron deficiency of the terminal nitrogen of the diazo group and depends in turn on the electron-attracting nature of the heterocyclic nucleus.⁸⁰

The diazonium salt derived from 5-amino-3-phenyl-1,2,4-thiadiazole attacks the unsaturated chain of a variety of heterocyclic polymethines,¹⁹⁵ particularly pyrrole- and cyanine-dyes, to yield products such as **299**. It also couples readily with a number of pyrroles; the effectiveness of the reagent exceeds that of diazotized trinitroaniline,

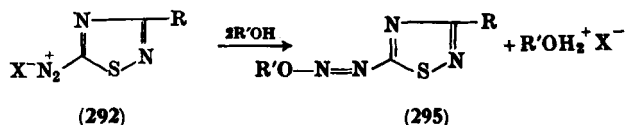
¹⁹⁵ A. Treibs and R. Zimmer-Galler, *Ann. Chem.* **627**, 166 (1959).

and is further demonstrated by its power to replace, by coupling, the iodine in 3-carbethoxy-4-iodo-2-methyl-5-nitropyrrrole, which resists the action of other diazonium salts.¹⁹⁵

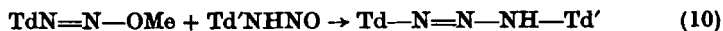


The stability and relatively ready accessibility of thiadiazole diazonium salts has encouraged their use in the production of numerous monoazo-dyes that have proved particularly suitable for dyeing polymers.^{192, 196}

b. *Action of Alcohols.*^{86, 169} Treatment of diazonium salts with alcohols, occasionally in acetonitrile solution, yields diazo-ethers (295). The reaction is reversible and may be made to go to completion by the use of a large excess of alcohol. The reaction is without parallel in the



benzene series, and appears to be made possible by the stabilizing influence of the heterocyclic nucleus on the diazo group. The diazo-ethers are devoid of coupling power: this is restored, however, in the presence of low concentrations of acids. Their condensation with nitrosamines yields triazens [Eq. (10)].¹⁶⁹

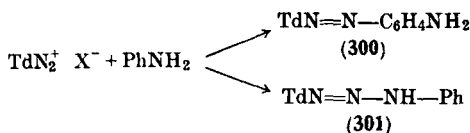


c. *Action of Amines.* Diazonium salts react with amines in acetonitrile almost instantly to yield triazens, a reaction that is particularly useful for the production of "mixed" triazens [Eq. (11)].

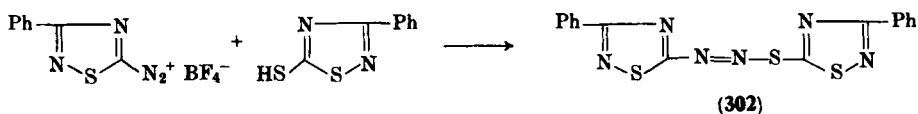


The use of aniline in this reaction yields, in addition to the triazen (301), the azo-dye 300, which may under certain conditions become the major product.¹⁶⁹

¹⁹⁶ K. Weis and H. Kleiner, British Patent 870,580 (1961); *Chem. Abstr.* **57**, 2371 (1962).

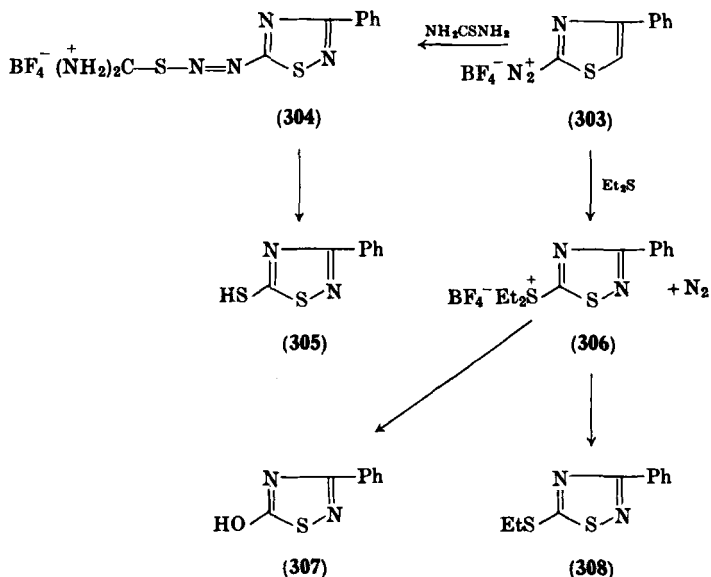


d. *Interaction with Compounds Incorporating Divalent Sulfur.* 3-Phenyl-1,2,4-thiadiazol-5-yl diazonium tetrafluoroborate reacts with 5-mercapto-3-phenyl-1,2,4-thiadiazole in acetonitrile to yield the azo compound **302**.



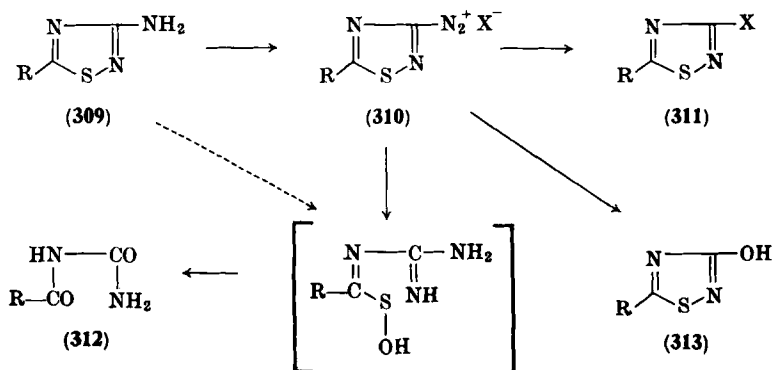
Reaction with thiourea results in salt-like *S*-azo compounds (**304**) that are sufficiently stable to be crystallized from boiling acetone. Further treatment with alkalis or excess thiourea results in their degradation to the thiol (**305**).¹⁶⁹

Interaction with diethyl sulfide occurs with simultaneous elimination of nitrogen and formation of a sulfonium salt of type **306**; its hydrolytic decomposition yields 5-hydroxy- (**307**) and 5-ethylthio-3-phenyl-1,2,4-thiadiazole (**308**), in proportions dependent upon the hydrogen ion concentration of the medium.¹⁶⁹

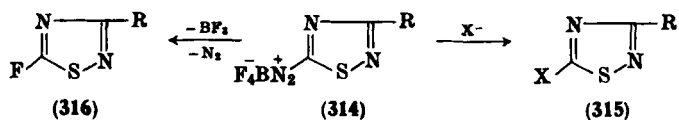


e. *Action of Halogen Ions.* In the Sandmeyer-Gattermann reaction, 5-amino-1,2,4-thiadiazole is converted into the 5-chloro or 5-bromo compound in 58 and 74 % yields, respectively.⁵ The 3-methyl homolog reacts analogously.⁵ This reaction has been extended¹⁷⁸ with limited success to the less reactive¹²⁶ 3-amino isomers. Diazotized 3-amino-5-phenyl-1,2,4-thiadiazole (**310**) is converted, in the presence of hydrohalogen acid and copper powder, into the 3-chloro or 3-bromo compound (**311**) in moderate yield¹⁷⁸ while substantial quantities of benzoylurea (**312**) and 3-hydroxy-5-phenyl-1,2,4-thiadiazole (**313**) are formed as by-products. The latter (**313**) arises directly from the diazonium salt (**310**), because it is not obtainable from the 3-chloro compound, once formed, and indeed becomes the main product of the diazotization under appropriate conditions. The 3-iodo compound (**311**; X = I) is unobtainable by this procedure, the 3-hydroxy analog being again the only product isolated.¹⁷⁸

Substituted amino groups in the 5-position interfere with the course of the reaction, possibly because of nitrosamine formation: thus, 3-amino-5-methylamino- and 3-amino-5-anilino-1,2,4-thiadiazole afford the corresponding 3-chloro derivatives (**311**; R = MeNH; PhNH; X = Cl) in only minute yields (5 and 8%, respectively).¹⁷⁸



3-Substituted 1,2,4-thiadiazol-5-yl diazonium tetrafluoroborates (**314**) react with potassium halides in acetonitrile in the absence of catalysts to afford the corresponding 5-halogeno compounds (**315**) in excellent yields.¹⁶⁹ The isomeric 5-phenyl-1,2,4-thiadiazol-3-yl diazonium salts, however, resist substitution by this procedure, except with iodide ions; by taking advantage of the catalytic effect of copper



salts, this difficulty may be overcome: thus, the use of the acetonitrile-soluble complex of cuprous chloride-lithium chloride (1:2) affords the 3-chlorothiadiazoles in 36% yield.¹⁶⁹ Finally, the 3-fluoro-5-phenyl- and 5-fluoro-3-phenyl-1,2,4-thiadiazoles (316) were obtained by the Balz-Schiemann reaction¹⁹⁷ pyrolytically from the appropriate diazonium tetrafluoroborates in 67 and 18% yields, respectively.¹⁶⁹

f. *Formation of Hydroxy Compounds.* Diazonium salts are converted into the corresponding hydroxy compounds in the presence of warm aqueous sulfuric acid. Thus, diazotization of 3-amino-5-phenyl-1,2,4-thiadiazole in 50% sulfuric acid at -10° , followed by gradual heating of the mixture, affords the hydroxy analog in 70% yield. The 5-*p*-nitrophenyl and 5-anilino analogs are similarly obtainable in approximately 40% yield.¹⁷⁸

Attempts to remove the amino group from 5-amino-1,2,4-thiadiazole by its reductive diazotization, in the presence of ethanol or hypophosphorous acid,¹⁹⁸ were not successful.

3. Diazonium Salts from 3-Amino-1,2,4-thiadiazoles

The 3-amino group in 1,2,4-thiadiazoles (e.g. in the 5-phenyl homolog) is also capable of being diazotized, preferably in concentrated phosphoric acid. The resulting diazonium salt may be coupled in the usual way, but with sufficiently reactive partners only (e.g. phenol and β -naphthol).¹²⁶

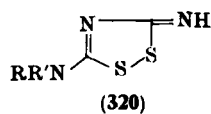
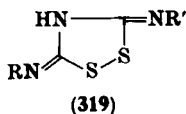
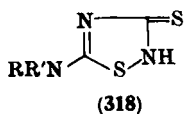
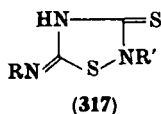
I. MERCAPTO-1,2,4-THIADIAZOLES

The oxidation of dithiobiuret and its homologs yields the so-called "thiurets" (for a summary, see ref. 134), for which a 1,2,4-dithiazolidine structure (319 and 320) is generally accepted. Their formulation as 3-thiono-1,2,4-thiadiazolidines (317 and 318) has been discussed,¹ but the weight of the available evidence supports the cyclic disulfide structure (319 and 320)¹³⁴ originally proposed.¹³³

5-Mercapto-1,2,4-thiadiazoles are distinctly acidic. The 3-methyl

¹⁹⁷ G. Balz and G. Schiemann, *Ber.* **60**, 1186 (1927).

¹⁹⁸ N. Kornblum, "Organic Reactions," Vol. 2, p. 262 *et seq.* Wiley, New York, 1944.



homolog has a pK value of 5.18 at 25° .⁸⁸ The 3-*p*-tolyl analog forms a salt with *p*-tolylamidine.^{71, 72}

5-Mercapto-3-phenyl-1,2,4-thiadiazole is stable, but is completely degraded by hydrochloric acid at 150° .⁷¹ It forms characteristic salts with metals, e.g. the crystalline mercury salt.^{71, 72, 190}

The action of aniline on 3-phenyl-5-mercapto-1,2,4-thiadiazole under restrained conditions is reported to remove the mercapto group as hydrogen sulfide, with formation of the corresponding 5-anilino compound.^{75, 200} This replacement, normally difficult in aromatic systems, may be due to the unusual reactivity of the thiol grouping in this particular structural environment.

Alkylation of mercapto groups in 1,2,4-thiadiazoles proceeds normally.^{71, 72} The reaction has provided authentic specimens of 3,5-dimethyl(or dibenzyl)mercapto-1,2,4-thiadiazoles, the identity of which with the *S*-alkylation products of perthiocyanic acid provided evidence concerning the structure of the latter compound⁹⁰ (see Section III, J,1).

1. Alkyl(and Aryl)thio-1,2,4-thiadiazoles

3-Alkylthio-1,2,4-thiadiazoles are stable steam-volatile compounds that may be purified by vacuum distillation.⁹⁹ Like their parent base, 1,2,4-thiadiazole, they form 1:1-adducts with metal salts, including silver nitrate and mercuric chloride.⁹⁹

3-Alkylthio-5-amino-1,2,4-thiadiazoles are generally insoluble in acids and alkalis, and resist desulfurization by alkaline sodium plumbite.¹³² The higher members are somewhat sensitive to hydrolysis^{85, 90}; the 3-phenylthio homolog is slowly destroyed by concentrated alkali, but its stability is much increased by acylation.⁸⁵

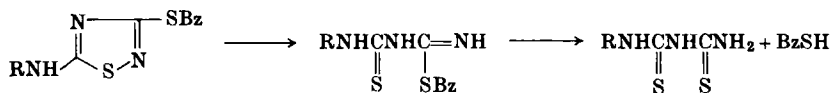
2. Reduction

Treatment of 5-alkyl(or aryl)amino-3-alkylthio-1,2,4-thiadiazoles with hydrogen sulfide in pyridine-triethylamine, or with sodium in liquid ammonia, yields 1-substituted dithiobiurets.¹³² Since, in the

¹⁹⁰ M. Kuraš, *Chem. Obzor.* **16**, 124 (1941); *Chem. Abstr.* **37**, 3023 (1943).

²⁰⁰ A. Barbos, *Ann. Sci. Univ. Jassy* **26**, 526 (1940); *Chem. Abstr.* **35**, 3254 (1941).

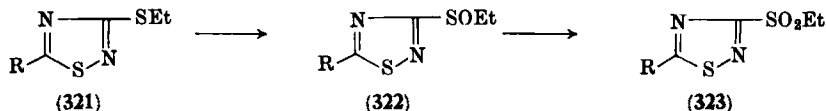
case of 3-benzylthio-5-methylamino-1,2,4-thiadiazole, 1-methyl-4-S-benzyliso-2,4-dithiobiuret may be isolated as the initial reduction product, the reaction probably occurs as follows¹³⁵:



Zinc and hydrochloric acid decompose 5-amino-3-phenylthio-1,2,4-thiadiazole with evolution of hydrogen sulfide and phenylthiol.⁸⁵

3. Oxidation

The sulfur in alkylthio groups of 1,2,4-thiadiazoles may be oxidized successively to the sulfoxide and sulfone stage. Thus, 5-amino(or anilino)-3-alkylthio-1,2,4-thiadiazoles (**321**; R = NH₂ or PhNH)^{85, 132} and 3-alkylthio-1,2,4-thiadiazoles (**321**; R = H),⁹⁹ on treatment with one or two moles of monoperphthalic acid, yield the appropriate oxidation products (**322** and **323**). Hydrogen peroxide or chlorine may replace the less convenient per-acid as the oxidizing reagent.⁸⁶ By careful



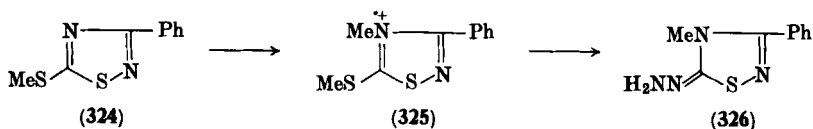
control of the conditions the reaction may be made to proceed to either desired stage in high yield.⁸⁶ The amino sulphones (**323**) thus obtained are marked by their pronounced acidity, their resistance to acylation, and their formation of stable nitrosamines, which are in turn converted into reactive diazonium salts under the influence of strong mineral or Lewis acids⁸⁶ (see Section III, E). While chlorine oxidizes alkylthio-1,2,4-thiadiazoles to sulfoxides and sulfones in aqueous suspension, it converts 3-benzylthio- into 3-chloro-5-amino-1,2,4-thiadiazole in glacial acetic acid⁸⁶ (see also ref. 168).

4. Aminolysis and Related Reactions

In accordance with the general stability of alkylthio groups in heteroaromatic systems, 3-alkylthio groups in 1,2,4-thiadiazoles are noteasily replaced. Thus, 3-alkylthio-1,2,4-thiadiazoles resist the action of aniline at 100°, ammonia at 120°, or molten urea or ammonium acetate.⁹⁹ On the other hand, hydrazine attacks 3-methylthio-1,2,4-thiadiazole under restrained conditions, with formation of 3-amino-

1,2,4-triazole in 85% yield.⁹⁹ In this case, the reaction may be initiated by a substituting action of the hydrazine, and then proceed as outlined for 1,2,4-thiadiazolyl-3-hydrazines (see Section III, G, 1).

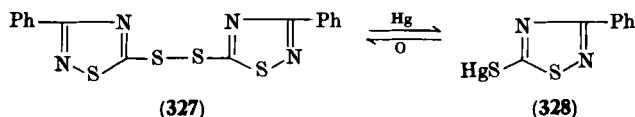
By successive quaternization of 3-phenyl-5-methylthio-1,2,4-thiadiazole (324) with dimethyl sulfate at 130°, and treatment with hydrazine hydrate, the hydrazone (326) is obtained; the oily material is advantageously isolated as the *p*-nitrobenzalazine.²⁰¹ This direct replacement by hydrazine in related heterocycles (e.g. 1,3,4-thiadiazoles, 1,2,4-triazoles, and tetrazoles) is rare, being usually achieved by the preliminary preparation of the acyl-hydrazone by means of benzoyl- or formyl-hydrazine, followed by acid hydrolysis of the intermediate acyl derivative.²⁰¹



5. Disulfides

5-Mercapto-1,2,4-thiadiazoles are oxidized, by 2*N* nitric acid at 50–60°, by chromic acid mixture, chlorine, or potassium permanganate to the disulfides, which are reconvertible to the thiols by reduction with sodium amalgam and alcohol.^{71, 72, 91, 168} Use of excess chlorine in aqueous acetic acid results in replacement of the mercapto group by the halogen.¹⁶⁸

The disulfide link is also opened by metallic mercury: thus, di(3-phenyl-1,2,4-thiadiazol-5-yl) disulfide (327) yields the corresponding mercaptide (328) which is changed back to the disulfide by treatment with iodine in organic solvents.¹⁵¹

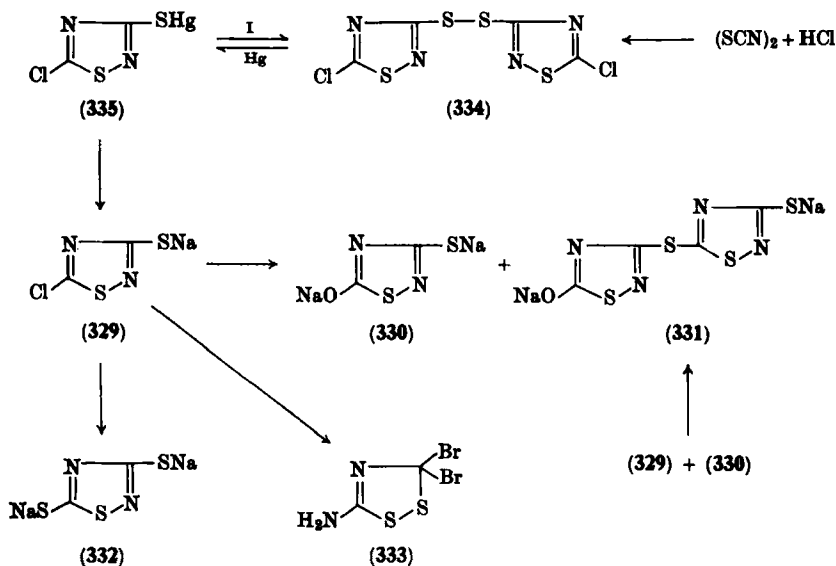


The corresponding reaction of (SCN)₄Cl₂^{201a} (334) affords a mercaptide (335), which is converted, on treatment with sodium sulfide, into a highly unstable sodium salt (329) probably of 5-chloro-3-mercapto-1,2,4-thiadiazole.¹⁵¹ With sodium hydroxide, this yields a mixture of

²⁰¹ S. Hünig and K. H. Oette, *Ann. Chem.* **641**, 94 (1961).

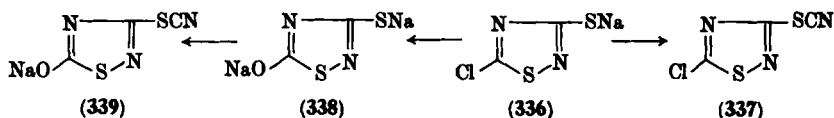
^{201a} For the origin and formulation of this compound from thiocyanogen and hydrogen chloride, see Section II, D, 2.

an insoluble form of polythiocyanogen, together with the disodium salt of 5-hydroxy-3-mercapto-1,2,4-thiadiazole (330) and a by-product, $C_4N_4OS_4Na_2$. Since the latter is also obtained by interaction of 329 and the main product (330), it has been formulated as 331.¹⁵¹ Further, the monosodium salt (329) yields, with sodium sulfide, the disodium salt of 3,5-dimercapto-1,2,4-thiadiazole (332) (i.e. disodium perthiocyanate).¹⁵¹ Hydrogen bromide (but not chloride) yields the dithiazolidine (333).¹⁵¹ This ring-transformation is explicable,^{151, 155} as being analogous to the reversible formation of isoperthiocyanic acid.¹⁴⁵ Each of the mercapto compounds 330 and 331 is smoothly convertible by iodine into the corresponding disulfide, which in turn reacts with mercury in the expected manner.¹⁵¹



The unstable sodium salt of 5-chloro-3-mercapto-1,2,4-thiadiazole (336)¹⁵¹ reacts also with cyanogen bromide forming 5-chloro-3-thiocyanato-1,2,4-thiadiazole (337).²⁰² The sparingly soluble neutral sodium salt of 5-hydroxy-3-thiocyanato-1,2,4-thiadiazole (339) is similarly obtained ($336 \rightarrow 338 \rightarrow 339$); its free acid, like other 5-hydroxy-1,2,4-thiadiazoles, is fairly strong, but unstable.²⁰²

²⁰² E. Söderbäck, *Svensk Kem. Tidskr.* **56**, 207 (1944).

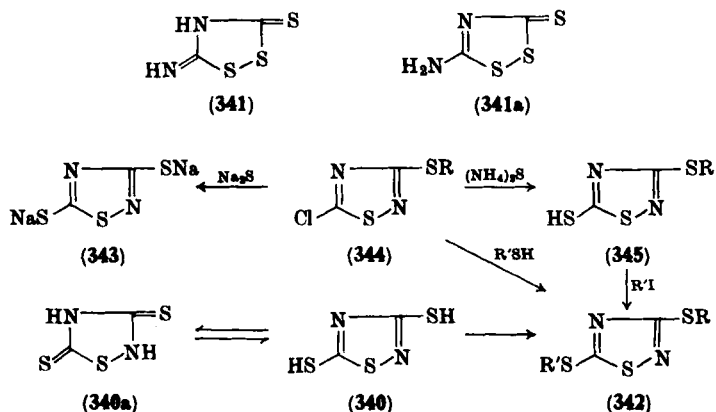


J. 3,5-DIMERCAPTO-1,2,4-THIADIAZOLES

1. The Structure of Perthiocyanic and Isoperthiocyanic Acid

The assignment of correct structures to isoperthiocyanic and perthiocyanic acid was a problem that presented great difficulties, aggravated by the ready interconversion of these isomeric compounds, and certain of their derivatives, into each other. The subject has been discussed in considerable detail by Sherman² and more particularly by Bambas,¹ who provided a full historical review and highlighted the confusion surrounding this problem. The present account is therefore mainly confined to recent results that have served to support the formulation of perthiocyanic acid as 3,5-dimercapto-1,2,4-thiadiazole (340). Iso-perthiocyanic acid, having the cyclic disulfide structure (341), is dealt with only in-so-far as it concerns perthiocyanic acid.

The structure (342; R, R' = Me or PhCH₂) of the di-*S*-ethers of perthiocyanic acid has been confirmed by Goerdeler and his co-workers.⁹¹ These compounds, which are the products of the alkylation of perthiocyanic acid (340) or its salts,^{144, 147} were unequivocally synthesized (i) by the interaction of 3-alkyl(or aralkyl)thio-5-chloro-1,2,4-thiadiazoles (344; R = Me or PhCH₂) with the appropriate thiols (R'SH)⁹¹, and (ii) by alkylation of the monoethers (345; R = Me or



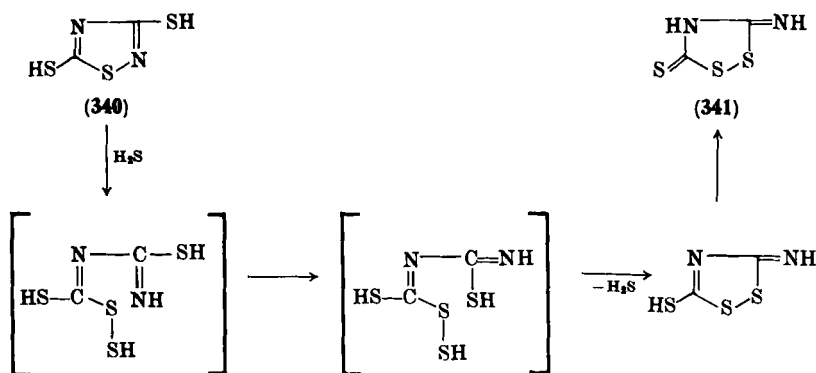
PhCH_2), obtained in their turn by treatment of 3-alkyl(or aralkyl) thio-5-chloro-1,2,4-thiadiazoles (**344**; $\text{R} = \text{Me}$ or PhCH_2) with ammonium sulfide.⁹¹ Additional support in favor of structure **340** for perthiocyanic acid is the alternative production of its disodium salt (**343**) from 5-chloro-3-mercapto-1,2,4-thiadiazole (**344**; $\text{R} = \text{Na}$) and sodium sulfide.¹⁵¹

The infrared spectra of the free acid and its barium salt¹⁵⁵ are in agreement with their being 1,2,4-thiadiazole derivatives; the presence of strong bands at 3010 and 2830 cm^{-1} , assigned to stretching vibrations of —NH— groups, suggests that the thiono configuration (**340a**) is preferred.¹⁵⁵

2. Properties of 3,5-Dimercapto-1,2,4-thiadiazoles

3,5-Dimercapto-1,2,4-thiadiazole is soluble in water and ether. Its water-soluble alkali salts are difficult to crystallize, but the barium salt, which forms several hydrates, may be purified by crystallization.¹⁴⁶ Heavy metal salts are often colored^{144, 203} and are soluble in potassium perthiocyanate solution.¹⁴⁴

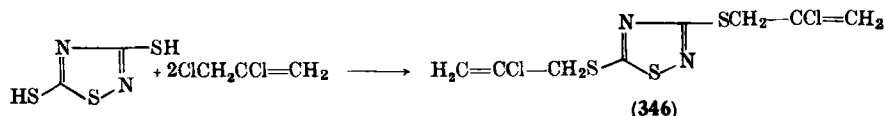
a. *Isomerization.* 3,5-Dimercapto-1,2,4-thiadiazole (**340**) changes readily into the non-acidic isoperthiocyanic acid (**341**), which is only sparingly soluble in water and ether, but crystallizes from 60% acetic acid as a yellow solid.^{144, 150} This rearrangement (see reaction scheme) is catalyzed by hydrogen sulfide, sulfurous acid, and compounds containing thiol groups, but is retarded by hydrochloric acid.¹⁴⁸



b. *S-Alkylation.* The alkylation by alkyl halides of 3,5-dimercapto-1,2,4-thiadiazole^{144, 147} and its mono-alkyl ethers⁹¹ proceeds normally.

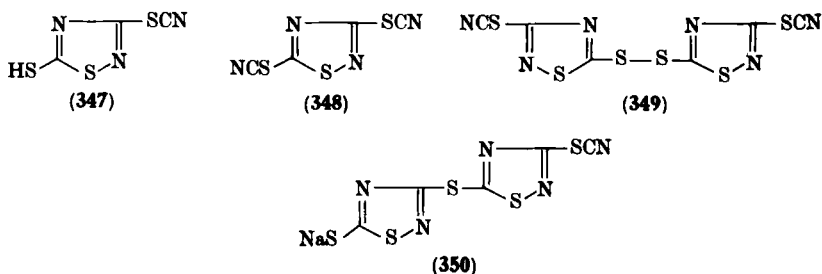
²⁰³ A. Fleischer, *Ber.* **4**, 190 (1871).

A number of 3,5-dihalogenoalkenyl-1,2,4-thiadiazoles (346) have been obtained²⁰⁴ by treatment of the dimercapto compound with dichloroalkenes (e.g. 2,3-dichloropropene) in aqueous sodium hydroxide. The reaction with chloroacetic acid yields 1,2,4-thiadiazolyl-3,5-di(thioglycollic) acid,¹⁴⁴ which forms salts and may be esterified in the usual way.



Di-*S*-ethers of 3,5-dimercapto-1,2,4-thiadiazole are generally very stable and can be steam-distilled. The weakly basic diethyl ether is dealkylated by alcoholic potassium hydrogen sulfide, but resists attack by alcoholic ammonia at 200°. Hydrogen chloride under pressure causes complete degradation.¹⁴⁴

c. *Thiocyanato Compounds*. The action of cyanogen bromide on 3,5-dimercapto-1,2,4-thiadiazole successively cyanogenates the mercapto groups; the precise structure of the resulting mercapto-thiocyanato-1,2,4-thiadiazoles and certain diheteryl mono- and di-sulfides derived therefrom are in part undecided (one possible alternative in each case being shown) (347–350).²⁰²



K. OTHER 1,2,4-THIADIAZOLE DERIVATIVES

1. Carboxylic Acids and Esters

The production of esters (179–181) from 5-chloro-3-methylthio-1,2,4-thiadiazole and esters containing active methylene groups, and their decarboxylation to 3-methylthio-1,2,4-thiadiazol-5-ylacetic acid is outlined in Section III, B, 1. The esterification of this acid by diazomethane, or ethanol-sulfuric acid, proceeds normally.⁹¹

²⁰⁴ M. W. Harman, U.S., Patent 3,058,990 (1962); *Chem. Abstr.* 58, 13965 (1963).

2. Thiocyanato-1,2,4-thiadiazoles

Mono- and di-thiocyanato-1,2,4-thiadiazoles, obtained by the stepwise action of cyanogen bromide on barium 3,5-dimercapto-1,2,4-thiadiazole, and on 5-chloro- and 5-hydroxy-3-mercapto-1,2,4-thiadiazole, are somewhat labile. The structures of certain of their transformation products (e.g. mono- and di-sulfides), which may have one of several isomeric forms, are not fully elucidated. The reactivity of their cyano group, resembling that in cyanogen halides, is noteworthy; it is easily removed by the action of alkalis, the parent thiol being regenerated.²⁰²

IV. Physical Properties

A. ISOSTERISM

As may be expected from the isosteric relationship between the two ring-systems, 1,2,4-thiadiazoles and the corresponding pyrimidine derivatives show certain similarities in their physical properties. Thus, the boiling points of the parent compounds are strikingly similar⁵ (see Table V).

TABLE V
BOILING POINTS OF PARENT BASES

1,2,4-Thiadiazole	b.p., 121°	Pyrimidine	b.p., 124°
1,3,4-Thiadiazole	204°	Pyridazine	208°

5-Amino-3-methyl-1,2,4-thiadiazole has a relatively high melting point and low solubility in water, compared with that of the 3-ethyl homolog and the parent compound; the isosteric 4-aminopyrimidines show a parallel behavior (see Table VI).⁶ 5-Amino-3-methoxy-1,2,4-thiadiazole melts at a higher temperature than does the ethoxy homolog.⁸³

The ionization constants of a number of 1,2,4-thiadiazoles have been determined potentiometrically^{87, 88} or by Hammett's method²⁰⁵ based on the measurement of ultraviolet absorption spectra in media of different hydrogen ion concentration.¹²⁶ The results are given in Table VII. 2- and 4-Aminopyrimidine differ in their basicities (pK_a

²⁰⁵ L. A. Flexser, L. P. Hammett and A. Dingwall, *J. Am. Chem. Soc.* **57**, 2103 (1935).

3.54 and 5.71, respectively); 3-amino-5-phenyl- and 5-amino-3-phenyl-1,2,4-thiadiazole exhibit a similar, though less pronounced, difference¹²⁶ (see Table VII).

TABLE VI
MELTING POINTS OF ISOSTERS

5-Amino-1,2,4-thiadiazoles				4-Aminopyrimidines		
	3-H	3-Me	3-Et	2-H	2-Me	2-Et
m.p.	119°	200°	117°	152°	208°	141°
		3-MeO	3-EtO			
m.p.		172°	105°			

TABLE VII
DISSOCIATION CONSTANTS OF 1,2,4-THIADIAZOLES

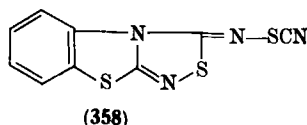
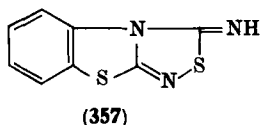
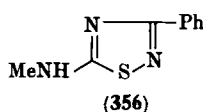
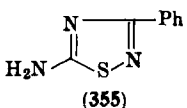
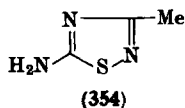
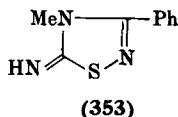
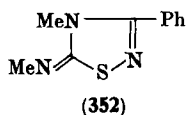
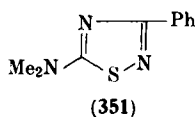
Derivative	pK_a	Reference
5-Amino-3-dimethylamino, hydrochloride	3.02	87
5-Amino-3-methyl, hydrochloride	2.57	87
3-Amino-5-phenyl	0.1	126
5-Amino-3-phenyl	1.4	126
3-Ethyl-5-hydroxy	6.89	88
3-Methyl-5-mercapto	5.18	88

B. ELECTROCHEMICAL PROPERTIES

In a systematic polarographic investigation¹⁸⁰ the half-wave potentials of a number of 1,2,4-thiadiazoles were determined and the results correlated with their structures. Measurements were made in neutral buffered solutions, the salt concentration being kept constant by the addition of lithium chloride.

Experiments using a series of methylated 2-amino-1,2,4-thiadiazoles of unequivocal structure (351–353) show that thiadiazoles (e.g. 351) are not reducible in methanolic lithium chloride solution, while thiadiazolines (e.g. 352–353) are uniformly reduced at $E_{0.5} = -1.6 \pm 0.02V$. In aqueous alcoholic tetramethylammonium iodide,

1,2,4-thiadiazoles are reduced at -2.16 V, and 1,2,4-thiadiazolines at -1.75 ± 0.01 V. Extension of this technique to compounds which may exist theoretically as either thiadiazoles or thiadiazolines (e.g. **354**–**356**) reveals that, being unreducible, they assume in fact the tautomeric thiadiazole form.¹⁸⁰ Moreover, the influence of substituents on



the reducibility of the 1,2,4-thiadiazole ring may be correlated with small changes in the observed half-wave potentials.¹⁸⁰

Other structures which have been confirmed polarographically are those of 5-imino-[benzthiazolo-(2,3-*b*)]-1,2,4-thiadiazoline (**357**) and *N*-thiocyanato-5-imino-[benzthiazolo-(2,3-*b*)]-1,2,4-thiadiazoline (**358**).¹⁸⁰ A polarographic technique has been employed¹⁶⁵ for demonstrating the absence of acidic hydrogen in 2,4-dimethyl-1,2,4-thiadiazolidine-3,5-dithione.

C. ULTRAVIOLET ABSORPTION SPECTRA

Ultraviolet absorption spectra of 1,2,4-thiadiazoles have been determined in increasing numbers in recent years, but the information so far available does not provide any broad correlation between structure and absorption characteristics.¹²²

Nevertheless, a comparison of the spectra of selected sets of compounds has helped in deciding structural questions in a number of cases. Thus, it has provided evidence for the existence of 5-amino-1,2,4-thiadiazoles⁸¹ and their nitroso derivatives¹⁷⁰ as enamines rather than ketimines, has supported the formulation of certain diazoamino-1,2,4-thiadiazoles¹⁹⁰ and pyrazolyl-1,2,4-thiadiazoles,¹¹² and has assisted in

a choice between possible structures of acylated 3-amino- and 3,5-diamino-1,2,4-thiadiazoles.¹²² Details are incorporated in the relevant sections of this chapter.

TABLE VIII

ULTRAVIOLET ABSORPTION SPECTRA OF 1,2,4-THIA DIAZOLES

Compound	References
1,2,4-Thiadiazole (parent base)	5
5-Alkyl(or aryl)-3-amino-1,2,4-thiadiazoles and homologs	122, 126
3-Alkyl(or aryl)-5-amino-1,2,4-thiadiazoles and homologs	6, 81
5-Alkyl(or aryl)amino-3-pyrazol-1'-yl-1,2,4-thiadiazoles	112
4-Alkyl-5-imino-1,2,4-thiadiazolines and homologs	81
5-Amino-3-hydroxy(or alkoxy or aryloxy)-1,2,4-thiadiazoles and homologs	122
5-Aryl-3-hydroxy-1,2,4-thiadiazoles	122
3-Alkylthio- 5-amino-1,2,4-thiadiazoles and homologs	122
Acyl derivatives thereof	122
3,5-Diamino-1,2,4-thiadiazoles and homologs	57, 63, 65, 87, 119, 120, 122
Acyl-derivatives thereof	122
5-Amino-3-imino-1,2,4-thiadiazolines and homologs	65, 115
3,5-Diimino-1,2,4-thiadiazolidines and homologs	65
3-Alkyl(or aryl)-5-nitrosamino-1,2,4-thiadiazoles and homologs	170
4-Methyl-5-nitrosimino-3-substituted-1,2,4-thiadiazolines	170
5-Alkyl(or aryl)amino-3-hydrazino-1,2,4-thiadiazoles	140
5-Arylamino-3-nitroamino-1,2,4-thiadiazoles	141
1,3-Bis[3-alkyl(or aryl)-1,2,4-thiadiazol-5-yl]triazens (Diazoamino-thiadiazoles)	190
1,2,4-Thiadiazol-5-yl azomethines	187
2,4-Dimethyl-1,2,4-thiadiazolidine-3,5-dithione	165
5-Carbethoxy-3-methyl-4-oxo-1-thia-2,3a,7-triazaindene	188

The parent compound, 1,2,4-thiadiazole, has an absorption maximum at 229 $m\mu$ ($\log \epsilon$ 3.7).⁵ As in benzene,²⁰⁶ the introduction of amino groups into the heteroaromatic 1,2,4-thiadiazole nucleus results in the bathochromic displacement of the absorption peak. Thus, the maximum due to 1,2,4-thiadiazole is moved to 247 $m\mu$ in 5-amino-⁸¹

²⁰⁶ E. A. Braude, *Ann. Rept. Progr. Chem. (Chem. Soc. London)* **42**, 105 (1942).

and to 256 $m\mu$ in 3,5-diamino-1,2,4-thiadiazole.¹²² The ultraviolet absorption spectra of numerous substituted 3,5-diamino-, 3-hydroxy-5-amino-, and 3-mercapto-5-amino-1,2,4-thiadiazoles, and the open-chain precursors from which they arise on oxidation, have been determined and discussed.¹²² Reference to these and other available data are given in Table VIII.

The ionization constants of 1,2,4-thiadiazoles can be determined by Hammett's method²⁰⁵ based on changes in their ultraviolet absorption spectra in media of different hydrogen ion concentration.¹²⁶

D. INFRARED ABSORPTION SPECTRA

Information concerning the infrared absorption spectra of 1,2,4-thiadiazoles is rather sparse, and existing data are listed in Table IX. Recent investigations have materially contributed to the elucidation of the structures of perthiocyanic and isoperthiocyanic acids and related compounds^{154, 155} (see Section III, J, 1) and of those of isothiocyanate oxides and sulfides¹⁶⁴ (see Section II, D, 3).

TABLE IX
INFRARED ABSORPTION SPECTRA OF 1,2,4-THIA DIAZOLES

Compound	References
1,2,4-Thiadiazole (parent base)	5
3,5-Diamino-1,2,4-thiadiazoles (aryl substituted)	65
5-Imino-4-phenyl-3-phenylimino-1,2,4-thiadiazolidine	65
5-Anilino-2-phenyl-3-phenylimino-1,2,4-thiadiazoline	65
1,3-Bis(3-ethyl-1,2,4-thiadiazol-5-yl)triazene	190
3-Methylthio-1,2,4-thiadiazole	99
5-Nitrosamino-3- <i>n</i> -propylmercapto-1,2,4-thiadiazole	170
3,5-Dimercapto-1,2,4-thiadiazole (perthiocyanic acid)	155
Isoperthiocyanic acid	154
2,4-Dialkyl-3-thiono-1,2,4-thiadiazolidin-5-ones	164
2,4-Dialkyl-1,2,4-thiadiazolidine-3,5-dithiones	164, 165

V. Physiological and Pharmacological Properties

Unlike their 1,3,4-isomers, 5-sulfanilamido-1,2,4-thiadiazoles containing branched-chain 3-substituents have no blood-sugar-reducing

properties.⁹² The patent literature claims their power of improving impaired liver function,¹⁷² and there is some indication that 3,5-diamino- and 5-amino-3-toluene-*p*-sulfonamido-1,2,4-thiadiazole may possess some hypoglycemic activity.¹⁸⁵

3-Ethyl(and ethoxy)-5-sulfonamido-1,2,4-thiadiazoles are effective against virus infections of the psittacosis-Lymphogranuloma inguinale group. Although exhibiting bacteriostatic activity *in vitro*,^{92, 93} they fail *in vivo*,⁹² possibly due to their strong affinity towards serum albumins.²⁰⁷ Antimicrobial properties are also shown by 3-mercapto-1,2,4-thiadiazole,²⁰⁸ 2,4-dimethyl-3-thiono-1,2,4-thiadiazolidin-5-one,¹⁶⁴ and 2,4-dimethyl-1,2,4-thiadiazolidine-3,5-dithione.¹⁶⁴

Fungicidal properties are exhibited by 3-methyl-²⁰⁹ and 3-methylthio-5-arylsulfonyl-1,2,4-thiadiazoles,²¹⁰ 5-substituted 3-trichloromethyl-1,2,4-thiadiazoles,⁹⁷ 2,4-dimethyl-3-thiono-1,2,4-thiadiazolidin-5-one,^{164, 166, 211} and 2,4-dimethyl-1,2,4-thiadiazolidine-3,5-dithione.^{165, 166} 5-Halogeno-3-halogenoalkyl-1,2,4-thiadiazoles are active against *Rhizoctonia solani*.⁹⁵

The fungicidal properties²¹² and production of albinism in plants²¹³ that have been referred to in connection with two 1,2,4-thiadiazoles are actually properties of the corresponding 1,3,4-isomers.²¹⁴

"Diethylmercuric perthiocyanate" possesses molluscicidal activity, as tested against the snail *Australorbis glabratus*, producing 100% mortality in 0.0003% concentration.²¹⁵ A mixture of isoperthiocyanic acid and 3,5-dimercapto-1,2,4-thiadiazole is effective against *Taenia* and *Dipylidium* in dogs, but is toxic to sheep, and without taeniacidal

²⁰⁷ W. Scholtan, *Arzneimittel-Forsch.* **11**, 707 (1961).

²⁰⁸ I. B. Simon and I. I. Kovtunovskaya-Levshina, Tiolovye Soedinen. v Med., Ukrain. Nauch.-Issledovatel. Sanit.-Khim. Inst., Trudy Nauch. Konf., Kiev 40 (1957) (pub. 1959); *Chem. Abstr.* **54**, 24760 (1960).

²⁰⁹ T. Noguchi, A. Kaji, S. Kosaka, and T. Murayama, Japanese Patent 17,997 (1962); *Chem. Abstr.* **59**, 11540 (1963).

²¹⁰ T. Noguchi, A. Kaji, K. Ishii, and S. Tabata, Japanese Patent 17,998 (1962); *Chem. Abstr.* **59**, 11540 (1963).

²¹¹ R. E. Allen, R. S. Shelton, and M. G. Van Campen, *J. Am. Chem. Soc.* **76**, 1158 (1954).

²¹² H. W. Gausman, C. L. Rhykerd, H. R. Hinderliter, E. S. Scott, and L. F. Audrieth, *Botan. Gaz.* **114**, 292 (1953).

²¹³ C. L. Rhykerd, H. W. Gausman, E. S. Scott, and L. F. Audrieth, *Science* **118**, 192 (1953).

²¹⁴ L. F. Audrieth, private communication (1963).

²¹⁵ H. W. Bond and M. O. Nolan, *Am. J. Trop. Med. Hyg.* **3**, 187 (1954); *Chem. Abstr.* **48**, 7839 (1954).

action.²¹⁶ 3-Aryl(or alkylthio or arylthio)-5-chloro-1,2,4-thiadiazoles⁹⁴ and analogous disulfides²¹⁷ are effective nematocides, as shown by their action against *Heterodera rostochiensis*, *Ditylenchus dipsaci*, and *Anguina tritici*.

The radioprotective action of 3,5-diamino-1,2,4-thiadiazole, its 3-toluene-*p*-sulfonyl derivative, and the corresponding 5-methyl-amino- and 5-anilino analogs has been determined.²¹⁸ Administration of the parent compound results in 69% survival in mice after 900 r whole body X-radiation, a result that compares favorably with the effects of such established protectors as AET (*S*-2-aminoethylthiuronium bromide hydrobromide) and cysteamine.²¹⁸

3,5-Diamino-1,2,4-thiadiazole is devoid of antithyroid activity, as measured by the effect of a single dose on the uptake of radioactive iodine by rat thyroid gland over a 4 hour period.²¹⁹

The inadequate nomenclature^{220, 221} employed in a number of papers, mostly of an applied character, makes it impossible to specify the particular 1,2,4-thiadiazole to which reference is being made²²¹; in some cases the distinction between 1,2,4- and 1,3,4-thiadiazoles is overlooked.²²⁰

VI. Uses

A. GENERAL

5-Amino-1,2,4-thiadiazoles⁷⁹ and their 3-alkoxy-, 3-alkylmercapto-, and 3-dialkylamino derivatives⁸⁴ have been claimed to be useful intermediates in the manufacture of dyes,⁸⁴ pharmaceuticals,⁸⁴ and materials valuable in pest control.⁷⁹ Mono-azo dyes derived from diazotized 5-amino-1,2,4-thiadiazoles and coupling components of the benzene series are especially suitable for dyeing polymeric materials such as acetate rayon, polyamides, polyurethanes, polyesters, and

²¹⁶ F. D. Enzie, *Proc. Helminthol. Soc. Wash., D.C.* **11**, 18 (1944); *Chem. Abstr.* **38**, 5967 (1944).

²¹⁷ E. H. Hambach and F. Herbold, German Patent 1,082,450 (1960); *Chem. Abstr.* **55**, 21,466 (1961).

²¹⁸ K. Stratton and E. M. Davis, *Intern. J. Radiation Biol.* **5**, 105 (1962).

²¹⁹ A. Lawson and C. E. Searle, *Biochem. J.* **59**, 345 (1955).

²²⁰ E. Jeney and T. Zsolnai, *Acta Microbiol. Acad. Sci. Hung.* **2**, 249 (1955); T. Ebina and M. Kurosu, *J. Natl. Cancer Inst.* **20**, 1023 (1958); O. J. Rafaelsen, *Metab. Clin. Exptl.* **8**, 195 (1959).

²²¹ H. F. Smyth, C. P. Carpenter, and C. S. Weil, *Arch. Ind. Hyg. Occupational Med.* **4**, 119 (1951); *Chem. Abstr.* **45**, 9710 (1951).

polyacrylonitriles. Blue, red, and yellow dyes are available that possess a high degree of light fastness.^{192, 196}

5-Mercapto-1,2,4-thiadiazole^{73, 222-224} and its analogs,²²⁴ as well as substituted 5-nitro (and nitroso) amino-1,2,4-thiadiazoles,¹⁸⁶ are effective antifoggants in photographic processes, providing a stabilizing and antifogging action without serious effect on speed or contrast.²²² The material may be incorporated in one of the layers of the photographic film, or applied in the developing bath.^{73, 224}

B. PERTHIOCYANIC ACID

The usefulness of 3,5-dimercapto-1,2,4-thiadiazole (perthiocyanic acid) has been claimed in a number of patents dealing with the manufacture and application of pigments,^{225, 226} protective paints,^{226, 227} and pesticides^{216, 228-231} of low phytotoxicity.²³¹ The actual reactant used is in fact frequently isoperthiocyanic acid,^{225, 226, 230, 232} but may in the course of the process be converted by alkalis into salts of perthiocyanic acid.^{226, 233} From solutions thus obtained may be produced ethers,^{219, 229} polysulfides,²²⁸ and heavy metal (including organomercury) salts.^{226, 227, 229, 231, 232}

3,5-Di(halogenoalkenylthio)-1,2,4-thiadiazoles are useful as defoliants, herbicides, insecticides, and rubber preservatives.²⁰⁴

²²² F. Dersch, F. J. Kaszuba, and E. B. Rauch, U.S. Patent 3,051,570 (1962); *Chem. Abstr.* **58**, 1084 (1963).

²²³ V. I. Sheberstov and B. A. Shashlov, *Zhur. Nauch. i Priklad. Fot. i Kinematograf.* **3**, 42 (1958); *Chem. Abstr.* **52**, 10775 (1958).

²²⁴ N. Nishio, M. Sugiyama, and K. Nasu, Japanese Patents 9710 (1960) and 9721 (1960); *Chem. Abstr.* **56**, 4290-4291 (1962).

²²⁵ W. H. Hill, U.S. Patent 2,402,962 (1946); *Chem. Abstr.* **40**, 5579 (1946).

²²⁶ W. H. Hill, U.S. Patent 2,402,961 (1946); *Chem. Abstr.* **41**, 605 (1947).

²²⁷ W. H. Hill, U.S. Patent 2,521,720 (1950); *Chem. Abstr.* **45**, 1162 (1951).

²²⁸ E. W. Bousquet and H. G. Guy, U.S. Patent 2,285,410 (1942); *Chem. Abstr.* **36**, 6744 (1942).

²²⁹ E. I. du Pont de Nemours & Co., British Patent 559,260 (1944); *Chem. Abstr.* **40**, 165 (1946).

²³⁰ H. Mengele, German Patent 721,633 (1942); *Chem. Abstr.* **37**, 4853 (1943).

²³¹ W. H. Hill, German Patent 895,673 (1953); *Chem. Abstr.* **52**, 14070 (1958).

²³² W. H. Hill, U.S. Patent 2,526,356 (1950); *Chem. Abstr.* **45**, 2501 (1951).

²³³ E. W. Bousquet, E. K. Ellingboe, and H. G. Guy, U.S. Patent 2,285,409 (1942); *Chem. Abstr.* **36**, 6744 (1942).

C. ANALYTICAL

3-Phenyl-5-nitrosamino-1,2,4-thiadiazole ("Phenitrazole") has been employed in analytical procedures. Phenols, aromatic amines, and aldehydes (as their phenylhydrazones) can be determined in γ -quantities, by being coupled with the diazo compound derived from this reagent, in the presence of perchloric acid; the resulting dyes exhibit maxima at 380–590 $m\mu$.²³⁴ A paper chromatographic technique²³⁵ and an estimation of urinary volatile phenols²³⁶ based on this method have been described.

The use of "Hector's base" (5-imino-4-phenyl-3-phenylimino-1,2,4-thiadiazolidine) as a sensitive reagent for carbon disulfide, and the nature of the product^{34, 50} formed by the interaction of these compounds have been discussed by Feigl *et al.*²³⁷

The determination of organic thiols, including dimercaptothiadiazole, by oxidation with 0.1*N* iodic acid in the presence of hydrochloric acid, has been described.²³⁸

²³⁴ M. Perez, J. Bartos, and J. F. Burtin, *Talanta* **5**, 213 (1960).

²³⁵ A. Sezerat, *Bull. Soc. Chim. France* 1193 (1961).

²³⁶ M. P. Zirinis, *Ann. Pharm. Franc.* **19**, 604 (1961).

²³⁷ F. Feigl, K. Weisselberg, and E. Klein, *Z. Anal. Chem.* **83**, 98 (1931).

²³⁸ G. Sandri, *Atti accad. sci. Ferrara* **35**, 105 (1957–58); *Chem. Abstr.* **54**, 18160 (1960).

The Aminochromes

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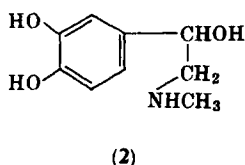
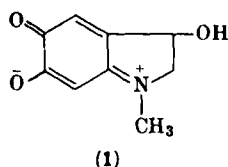
1. Introduction

The deep red to violet colored compounds obtained on oxidation of catecholamines are known as the aminochromes¹ and have attracted

¹ H. Sobotka and J. Austin, *J. Am. Chem. Soc.* **73**, 3077 (1951).

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considerable attention in recent years, not only from organic chemists and biochemists, but also from research workers in the pharmacological, physiological, and medical fields. Three previous reviews which have appeared on this subject give, between them, a comprehensive survey of the literature on the aminochromes through 1958.²⁻⁴ The object of the present review is to bring the reader up-to-date with the latest developments in this field. For the purposes of this article, the definition of the term aminochrome is restricted to that originally proposed by Sobotka and Austin for the 2,3-dihydroindole-5,6-quinone derivatives [e.g. adrenochrome: the zwitterionic form (1) of these compounds is believed to predominate in the resonance hybrid^{5,6}] obtained on oxidation of 3,4-dihydroxyphenylethylamines [e.g. adrenaline (2)].¹ A number of other chemically similar, but structurally slightly different, substances are considered briefly in Section VI.



II. Aminochrome Formation

A. OXIDATIONS OF CATECHOLAMINES IN DILUTE SOLUTION

1. General Comments

The oxidations in dilute solution discussed in this section mostly involve molecular oxygen as the oxidizing agent. The oxidative step in several catecholamine assay procedures, which usually involves the participation of an inorganic oxidizing agent, and which also occurs "in dilute solution," is considered in Section V, E.

There is still not complete agreement as to whether catecholamines undergo a true autoxidation in dilute aqueous solution at neutral

² H. Sobotka, N. Barsel, and J. D. Chanley, *Fortschr. Chem. Org. Naturstoffe* **14**, 217 (1957).

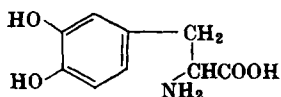
³ R. A. Heacock, *Chem. Rev.* **59**, 181 (1959).

⁴ A. Correia Alves, *Anais Fac. Farm. Porto* **19**, 21 (1959).

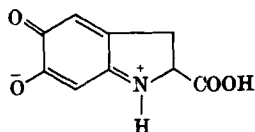
⁵ J. Harley-Mason, *Experientia* **4**, 307 (1948).

⁶ J. Harley-Mason, *J. Chem. Soc.* 1276 (1950).

pH's (see refs. 2 and 3 for a review of the earlier literature). However, evidence has been presented that DOPA [3,4-dihydroxyphenyl-alanine⁷ (3)] and adrenaline (2) probably undergo a true autooxidation in the apparent absence of metal ions,⁸⁻¹⁰ although there is not complete agreement about the subsequent catalysis of the oxidation by the aminochromes formed [i.e. dopachrome (4) and adrenochrome



(3)



(4)

(1), respectively^{8, 10}], as had been previously reported.^{11, 12} Catecholamines are rapidly oxidized by atmospheric oxygen at alkaline pH (cf. refs. 2 and 3); however, borates protect adrenaline from oxidation at pH's below 9.0, presumably by complex formation with the *o*-dihydroxy group.¹³

As a result of kinetic studies carried out on the oxidation of adrenaline with molecular oxygen at pH 5 in acetate buffer, Sokoloski and Higuchi¹⁰ concluded that the reaction was relatively complex and involved free radical intermediates. At low concentrations of both adrenaline and oxygen, the reaction was effectively first order with respect to both components. With high concentrations of both reactants the orders with respect to oxygen and adrenaline were said to be < 0.5 and 0.5, respectively, the appearance of fractional orders being indicative of free radical-mediated sequences.

2. Metal-Catalyzed Oxidations

It has been known for many years that some metal ions and metal-containing proteins (e.g. ceruloplasmin and ferritin) readily catalyze

⁷ Although it might not be strictly regarded as a catecholamine, DOPA will be considered as a catecholamine for the purposes of this review.

⁸ C. Monder, J. N. Williams, and H. A. Waisman, *Arch. Biochem. Biophys.* **72**, 255 (1957).

⁹ C. Monder, J. N. Williams, and H. A. Waisman, *Arch. Biochem. Biophys.* **72**, 271 (1957).

¹⁰ T. D. Sokoloski and T. Higuchi, *J. Pharm. Sci.* **51**, 172 (1962).

¹¹ J. E. Falk, *Biochem. J.* **44**, 369 (1949).

¹² E. M. Trautner and T. R. Bradley, *Australian J. Sci. Res.* **4B**, 303 (1951).

¹³ E. M. Trautner and M. Messer, *Nature* **169**, 31 (1952).

the oxidation of catecholamines in dilute solution (see refs. 2 and 3 for reviews of the early literature). Walaas *et al.*¹⁴ have recently shown spectroscopically that in the complexes obtained from adrenaline and noradrenaline with Cu^{++} ions two catecholamine residues are complexed by one Cu^{++} ion, and that the ultraviolet absorption spectrum of this complex resembles that of the catechol-amine ion. These complexes were stable under anaerobic conditions but rapidly autoxidized in the presence of oxygen with the formation of adrenochrome and noradrenochrome, respectively,¹⁴ thus confirming the earlier reports of Chaix *et al.*^{15, 16} Litwack recently described the complex formed from adrenaline with Fe^{++} ions; this is also a 2:1 catecholamine-metal ion complex.¹⁷ This complex was apparently stable at neutral and mildly acid pH's, but at elevated pH's (i.e. *ca.* 9.5) it appeared to autoxidize with the formation of adrenochrome.¹⁷ Vanadium salts and/or metallic vanadium exert a powerful catalytic effect on the oxidation of several catecholamines, including adrenaline, noradrenaline, dopamine, and DOPA.^{18, 19} Flesch *et al.* reported that EDTA severely retards the metal-catalyzed oxidation of adrenaline, the extent depending on the nature of the catalyst and the buffer used.²⁰

Considerable interest has arisen recently in the oxidation of catecholamines by metal-containing proteins and certain metal complexes with organic compounds which might serve as "enzyme models." The most extensively studied member of this interesting group of substances is the blue copper-containing protein known as ceruloplasmin. One of the earliest reports of the oxidizing activity of this compound with respect to catecholamines was that of Holmberg and Laurell in 1951²¹; it has subsequently been shown by several workers that all catecholamines are readily oxidized to the corresponding aminochromes in the presence of ceruloplasmin.²²⁻²⁶ Curzon

¹⁴ E. Walaas, O. Walaas, S. Haavaldsen, and B. Pedersen, *Arch. Biochem. Biophys.* **100**, 97 (1963).

¹⁵ P. Chaix, J. Chauvet, and J. Jézequel, *Biochim. Biophys. Acta* **4**, 471 (1950).

¹⁶ P. Chaix and C. Pallaget, *Biochim. Biophys. Acta* **10**, 462 (1953).

¹⁷ G. Litwack, *Life Sciences* **509** (1962).

¹⁸ G. M. Martin, E. P. Benditt, and N. Eriksen, *Federation Proc.* **18**, 492 (1959).

¹⁹ G. M. Martin, E. P. Benditt, and N. Eriksen, *Nature* **186**, 884 (1960).

²⁰ C. Flesch, W. Schuler, and R. Meier, *Helv. Chim. Acta* **43**, 2014 (1960).

²¹ C. G. Holmberg and C. B. Laurell, *Acta Chem. Scand.* **5**, 476 (1951).

²² E. Walaas and O. Walaas, *Arch. Biochem. Biophys.* **95**, 151 (1961).

reported that the oxidation of adrenaline by ceruloplasmin was partly inhibited by EDTA, but enhanced by ferrous iron.²⁵ Geller *et al.* observed that no oxygen uptake occurred when certain catecholamines, including those mentioned above, were incubated with ceruloplasmin at pH 6; however, color formation, not necessarily indicative of the formation of oxidation products, was occasionally observed.²⁶ These workers confirmed earlier observations¹⁵ that the Cu^{++} -ion-catalyzed oxidation is pH-dependent, being faster at mildly alkaline pH. They did, however, suggest that ceruloplasmin inhibits the copper-catalyzed oxidation of adrenaline at pH 7.4.²⁶ In a recent thorough physico-chemical study of the interaction of catecholamines with ceruloplasmin, Walaas *et al.* have shown that the blue color of the protein is discharged rapidly on addition of the substrate, indicating that the copper present in the protein is being reduced from the cupric to the cuprous state.^{14, 22-24} The rate of this reaction was followed spectroscopically by the disappearance of the 605 $\text{m}\mu$ absorption peak of ceruloplasmin and the decrease in the intensity of the E.S.R. signal obtained from the protein on addition of catecholamine.^{23, 24} The rate of decolorization of ceruloplasmin was shown to vary with the substrate used and is in the order dopamine > noradrenaline > adrenaline > *N*-isopropylnoradrenaline > DOPA.²⁴ The rate is slightly accelerated by the presence of oxygen.²⁴ The nature of the catecholamine side chain had an important bearing on the interaction with the protein, apparently being hindered by *N*-alkylation and by the 2-carboxyl group.²⁴ The initial oxidation product of the catecholamine, which was said to be free-radical or quinonoid in nature, was capable of further dehydrogenation in the presence of oxygen to give the corresponding aminochrome. These workers further showed that the overall rate of oxidation of several catecholamines to the corresponding aminochromes by ceruloplasmin is, by contrast, in the order adrenaline > *N*-isopropylnoradrenaline > noradrenaline > dopamine.²³ Copper-containing plasma protein complexes have been claimed to be more efficient catalysts for DOPA oxidation than are Cu^{++} ions.⁹ The catalysis of DOPA oxidation by copper and iron complexes of

²³ E. Walaas and O. Walaas, *Acta Chem. Scand.* **17**, 897 (1963).

²⁴ O. Walaas, E. Walaas, T. Henriksen, and R. Lövsstad, *Acta Chem. Scand.* **17**, S263 (1963).

²⁵ G. Curzon, *Biochem. J.* **79**, 656 (1961).

²⁶ E. Geller, S. Eiduson, and A. Yuwiler, *J. Neurochem.* **5**, 73 (1959).

L-histidine, L-glutamine, and L-histidine anhydride²⁷ and by copper complexes of organic bases such as *o*-phenanthroline and α, α' -dipyridyl has also been reported; these complexes were more active than Cu^{++} ions alone.²⁸

3. Enzymic Oxidation

The oxidation of DOPA and adrenaline to dopachrome and adrenochrome, respectively, by a horse radish peroxidase- H_2O_2 system has been reported by Herzmann.^{29, 30} The oxidation process was activated by trace quantities of caffeic acid, its esters, and related compounds.³⁰ Ascorbic acid inhibited the oxidation of adrenaline by this enzyme in the initial stages of the reaction, but later had a stimulatory effect.³⁰

The oxidation of catecholamines in the presence of tyrosinases and polyphenolases has been widely studied, and the subject has been adequately discussed in the literature. References 12 and 31-41 will serve as a guide to further reading on the subject.

There has been some controversy in the literature about the possibility of there being an enzyme system in mammalian body fluids or tissues capable of oxidizing adrenaline to adrenochrome. The claim of Payza and Hoffer that serum oxidizes adrenaline enzymically to adrenochrome⁴² has been queried by Geller *et al.*²⁶

²⁷ G. Losse, A. Barth, and W. Langenbeck, *Chem. Ber.* **94**, 2271 (1961).

²⁸ S. Isaka, *J. Biochem. (Tokyo)* **47**, 733 (1960).

²⁹ H. Herzmann, *Naturwissenschaften* **44**, 377 (1957).

³⁰ H. Herzmann, *Z. Physiol. Chem.* **315**, 285 (1959).

³¹ J. M. Nelson and C. R. Dawson, *Advan. Enzymol.* **4**, 99 (1944).

³² Z. M. Bacq, *J. Pharmacol. Exp. Therap.* **95**, Part II. *Pharmacol. Rev.* **1**, 1 (1949).

³³ A. B. Lerner, *Advan. Enzymol.* **14**, 73 (1953).

³⁴ H. S. Mason, *Advan. Enzymol.* **16**, 105 (1955).

³⁵ T. L. Sourkes, *Rev. Can. Biol.* **17**, 328 (1958).

³⁶ U. S. von Euler, *Recent Progr. Hormone Res.* **14**, 491 (1958).

³⁷ K. T. Yasunobu, in "Pigment Cell Biology" (M. Gordon, ed.), p. 583. Academic Press, New York, 1959.

³⁸ S. Ya. Kaplanskii and C.-Y. Wang, *Voprosy Med. Khim.* **7**, 227 (1961); *Chem. Abstr.* **55**, 23608 (1961).

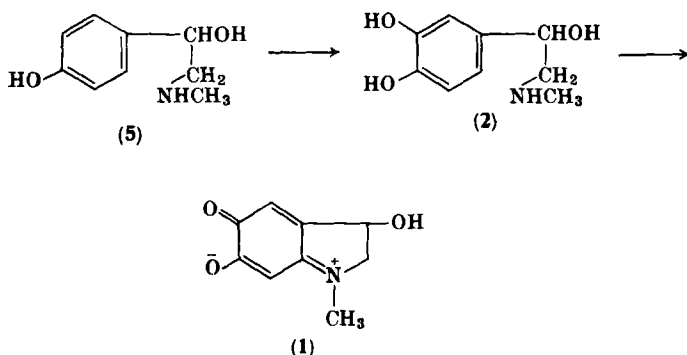
³⁹ D. Kertesz and R. Zito, *Biochim. Biophys. Acta* **64**, 153 (1962).

⁴⁰ H. J. Bright, B. J. B. Wood, and L. L. Ingraham, *Ann. N. Y. Acad. Sci.* **100**, 965 (1963).

⁴¹ S. Osaki, *Arch. Biochem. Biophys.* **100**, 378 (1963).

⁴² A. N. Payza and A. Hoffer, *Bull. Fac. Med. Istanbul* **22**, 1096 (1959); *Chem. Abstr.* **54**, 15607 (1960).

However, Van der Wender and Spoerlein have recently described the presence of an enzyme system in rat brain that is capable of oxidizing DOPA to melanitic pigments⁴³ (an aminochrome, i.e. dopachrome, must be formed as an essential intermediate in this process); the same enzyme system apparently oxidizes adrenaline to adrenochrome.⁴³ Kaliman has demonstrated the presence of an enzyme system in rabbit heart tissue which oxidizes adrenaline via the "quinonoid pathway" (presumably to adrenochrome).⁴⁴ Heart, kidney, and brain tissues of white rats were also shown by Kaliman and Koshlyak to possess similar activity.⁴⁵



Recently adrenochrome has been obtained (as its semicarbazone) by the air oxidation of synephrine [i.e. β-(4-hydroxyphenyl)ethylmethanamine (5)] in the presence of potato tyrosinase.⁴⁶ This overall reaction must involve an initial hydroxylation of synephrine (5) to give adrenaline (2), which is subsequently oxidized to adrenochrome (1).

The oxidation of tyrosine-containing proteins and peptides in the presence of tyrosinase has been studied by several workers.^{47, 48} Yasunobu *et al.* differentiated between the three possible oxidative

⁴³ C. Van der Wender and M. T. Spoerlein, *Life Sciences* 386 (1963).

⁴⁴ P. A. Kaliman, *Biokhimiya* 26, 284 (1961); *Chem. Abstr.* 55, 16732 (1961).

⁴⁵ P. A. Kaliman and T. V. Koshlyak, *Biokhimiya* 26, 729 (1961); *Chem. Abstr.* 55, 27582 (1961).

⁴⁶ A. Terada, *Nippon Kagaku Zasshi* 81, 757 (1960); *Chem. Abstr.* 56, 370 (1962).

⁴⁷ I. W. Sizer, *Advan. Enzymol.* 14, 129 (1953).

⁴⁸ K. T. Yasunobu, E. W. Peterson, and H. S. Mason, *J. Biol. Chem.* 234, 3291 (1959).

pathways open to peptides with molecular weights of up to *ca.* 4,600 spectroscopically.⁴⁸ With *N*-terminal tyrosine peptides a "dopachrome" pathway was established, which is characterized by the formation of an intermediate oxidation product containing "dopachrome" units and exhibiting the characteristic "dopachrome" absorption maxima at 305 and 480 $m\mu$ in the initial stages of the reaction. This absorption pattern was superseded by one showing a single peak at 325 $m\mu$, characteristic of the expected 2-carboxy-5,6-dihydroxyindole chromophore. Small *C*-terminal tyrosine peptides were oxidized via the "dopa-quinone" pathway. In this case the characteristic *o*-quinone absorption at 390 $m\mu$ was observed; the intermediate products, which were unable to undergo the normal cyclization to dopachrome, eventually decomposed slowly by a different route. Peptides of higher molecular weight, in which both the amino and carboxyl groups of the tyrosine residues were substituted, were oxidized by the "protein" pathway. This pathway was less well defined, but in some cases products absorbing in the 350 $m\mu$ region were observed.⁴⁸ Rolland and Lissitzky have also reported recently that dopaquinone units are formed during the oxidation of tyrosine-containing peptides and proteins by mushroom polyphenol-oxidase^{49, 50}; these units may be stabilized when included in the peptide chain (cf. ref. 48).

4. Radiation-Induced Oxidation

In 1937 Arnow showed that tyrosine could be converted into DOPA by ultraviolet radiation⁵¹ and that the DOPA produced in this manner was subsequently destroyed by further irradiation, the solutions becoming red-brown in color (presumably due to the formation of dopachrome).⁵¹ In 1939 Konzett and Weis reported that the blood pressure-raising effect of adrenaline solutions was lost on ultraviolet irradiation and that the solutions became colored and fluorescent; the initial red color fades to reddish yellow.⁵² This phenomenon suggests the initial formation of adrenochrome, followed by its isomerization to adrenolutin, both of these compounds being virtually void of pressor activity. Similarly to the radiation-induced hydroxylation of tyrosine mentioned above, synephrine was first

⁴⁸ M. Rolland and S. Lissitzky, *Biochim. Biophys. Acta* **56**, 83 (1962).

⁵⁰ S. Lissitzky and M. Rolland, *Biochim. Biophys. Acta* **56**, 95 (1962).

⁵¹ L. E. Arnow, *J. Biol. Chem.* **120**, 151 (1937).

⁵² H. Konzett and W. Weis, *Arch. Exp. Pathol. Pharmacol.* **193**, 440 (1939).

hydroxylated to give adrenaline, which subsequently decomposed under the influence of further radiation in the manner previously described.⁵² Similar findings were reported by Chatonnet and Vial, i.e. that irradiated solutions of adrenaline became red in color and lost their pressor effects.⁵³ Recent work by Johnson on the effects of ultraviolet irradiation of tyrosine has suggested that more complex reactions may occur under certain conditions.⁵⁴ Although addition of tyrosinase to the irradiated solutions caused a rapid oxygen uptake to occur, it was not possible, according to Johnson, to induce non-enzymic melanization of tyrosine by irradiation alone.⁵⁴ The initial products were golden yellow in color; on continued irradiation the color deepened somewhat at first and then eventually disappeared with an appreciable concomitant oxygen uptake.⁵⁴ (Dopaquinone and 5,6-dihydroxyindole were said to be present in solutions which had been irradiated briefly.) The yellow substance (λ_{\max} 245 and 300–305 m μ) could be extracted from solution with isobutanol, and several of its properties suggested that it was an ommatin pigment. The 2,3-bond of the pyrrole ring of the dihydroindole nucleus was split by radiation-induced oxidation to give an *o*-aminophenol derivative, which condensed with a dopaquinone unit to form the ommatin pigment.⁵⁴

In addition to oxidative deamination, X-irradiation of tyrosine or DOPA solutions, in air, gave rise to the formation of indole derivatives, presumably via the dopachrome pathway, since the solutions initially became red in color, then brown, and finally a black precipitate of a melanin formed (Nosworthy and Allsopp).⁵⁵ Previously other workers had observed similar changes on irradiation of tyrosine solutions with X-rays and with α - and γ -rays.^{56, 57} 8-Methoxypsoralen (8-MOP) (a furocoumarin used for promoting sun tanning) stimulated the oxidation of DOPA to dopachrome under the influence of sunlight, white light, or long-wave ultraviolet light.⁵⁸ However, 8-MOP protected DOPA against the action of short-wave ultraviolet light, although this form of radiation stimulated the oxidation of DOPA alone.⁵⁸ In recently reported animal studies it was claimed that

⁵³ J. Chatonnet and J. Vial, *Compt. Rend. Soc. Biol.* **139**, 112 (1945).

⁵⁴ M. B. Johnson, *Nature* **190**, 924 (1961).

⁵⁵ J. Nosworthy and C. B. Allsopp, *J. Colloid Sci.* **11**, 565 (1956).

⁵⁶ C. E. Nurnberger, *Proc. Natl. Acad. Sci. U. S.* **23**, 189 (1937).

⁵⁷ J. Rowbottom, *J. Biol. Chem.* **212**, 877 (1955).

⁵⁸ J. Judis, *J. Am. Pharm. Assoc., Sci. Ed.* **49**, 447 (1960).

internal or external X-radiation (or γ -radiation) lowers the adrenaline content of various tissues with the concomitant appearance of oxidation products of adrenaline.^{59, 60}

The chemical transformations that occur on ultraviolet irradiation of adrenaline and noradrenaline solutions have been investigated by Walaas, who showed that the initial photoactivation of the catecholamine molecule is a direct effect (i.e., it is not dependent on the presence of trace metals) and that the activated species, probably free radical in nature, are readily autoxidizable in air.⁶¹ Walaas suggests that the activation of catecholamines by ultraviolet radiation may involve electronic changes similar to those initially occurring during the metal-catalyzed oxidation of catecholamines at an intermediate pH.^{14, 61}

At neutral pH adrenaline was oxidized first to adrenochrome and then to melanin; different products were produced at alkaline pH and melanin formation was low. With noradrenaline similar processes took place at neutral pH, but at a slower rate; in this case the alkaline oxidation was characterized by increased melanin formation.⁶¹

Adrenaline and noradrenaline were oxidized in solution by hydrogen peroxide in the absence of metals via a free radical mechanism on irradiation. However, no aminochrome formation was observed.⁶¹

B. PREPARATIVE PROCEDURES

The main procedure used for the preparation of adrenochrome (1) in the laboratory involves the oxidation of adrenaline by silver oxide in methanol. This method, which was first described by Veer in 1942^{62, 63} and subsequently used by many other workers (see refs. 2 and 3 for early references), is still the simplest procedure available for obtaining adrenochrome (1) and similar non-halogenated amino-

⁵⁹ L. I. Polikarpova, *Radiobiologiya* **1**, 899 (1961); *Chem. Abstr.* **56**, 14585 (1962).

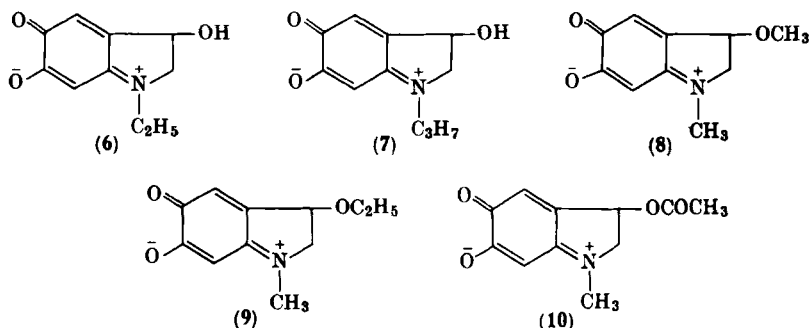
⁶⁰ E. N. Petrovnina, *Radiobiologiya* **1**, 907 (1961); *Chem. Abstr.* **56**, 14585 (1962).

⁶¹ E. Walaas, *Photochem. Photobiol.* **2**, 9 (1963).

⁶² W. L. C. Veer, *Rec. Trav. Chim.* **61**, 638 (1942).

⁶³ Seven years previously S. Weinstein and R. J. Manning [*Proc. Soc. Exptl. Biol. Med.* **32**, 1096 (1935)] had obtained a red crystalline product from the oxidation of adrenaline by silver oxide, but they erroneously described it as the hypothetical adrenaline-quinone.

chromes in crystalline form and usually gives satisfactory results. The reported instability of the adrenochrome obtained by early workers in this manner was probably due to contamination of the product with residual silver.⁶⁴ The procedure introduced in 1958 by Heacock *et al.* for the preparation of adrenochrome, which involves filtering the reaction mixture through an anion exchange resin in the chloride form immediately prior to crystallization, gives good yields of a pure, stable, and relatively silver-free crystalline product.⁶⁴ This procedure has recently been successfully applied by Heacock and Scott to the preparation of *N*-ethylnoradrenochrome (6) and *N*-isopropylnoradrenochrome (7).⁶⁵



Adrenochrome methyl and ethyl ethers (8 and 9 respectively), first isolated by Hukki and Seppäläinen as their semicarbazones,⁶⁶ have now been obtained in crystalline form by oxidation of the corresponding catecholamine ethers with silver oxide in dry acetonitrile.⁶⁵ *N*-Ethylnoradrenochrome (6) has also been prepared in crystalline form by the oxidation of *N*-ethylnoradrenaline in 90% methanol with the calculated quantity of iodic acid⁶⁵ (cf. the preparation of adrenochrome by Mácciotta⁶⁷). Adrenochrome *O*³-acetate (3-acetoxyepinochrome) (10) was obtained by the oxidation of "acetyladrrenaline" [β -acetoxy- β -(3,4-dihydroxyphenyl)ethylmethylamine].⁶⁸

⁶⁴ R. A. Heacock, C. Nerenberg, and A. N. Payza, *Can. J. Chem.* **36**, 853 (1958).

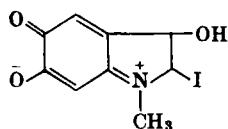
⁶⁵ R. A. Heacock and B. D. Scott, *Can. J. Chem.* **38**, 516 (1960).

⁶⁶ J. Hukki and N. Seppäläinen, *Acta Chem. Scand.* **12**, 1231 (1958).

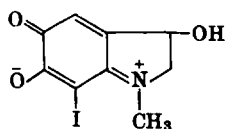
⁶⁷ E. Mácciotta, *Gazz. Chim. Ital.* **81**, 485 (1951).

⁶⁸ W. Schoeller, J. Jonás, and P. Marquardt, German Patent 866,039 (1953); *Chem. Abstr.* **52**, 16369 (1958).

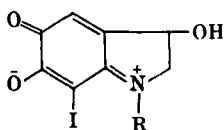
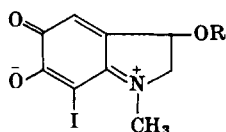
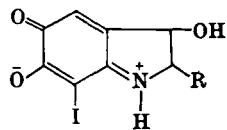
The oxidation of adrenaline with excess potassium iodate in unbuffered aqueous solution gives a violet-brown solid; this solid was first obtained by Richter and Blaschko in 1937 and considered to be 2-iodoadrenochrome (11).⁶⁹ The iodine atom in the iodoaminochromes (or the bromine atom in bromoadrenochrome) has recently been shown to occupy the 7-position in the aminochrome molecule,⁷⁰ rather than the 2-position as originally believed. Consequently, the iodoadrenochrome referred to above should be formulated as a 7-iodo derivative (i.e., as 12). The iodoaminochromes presumably arise by iodination of the initially formed aminochromes (cf. ref. 3).



(11)



(12)

13A; R = C₂H₅13B; R = *i*-C₃H₇14A; R = CH₃14B; R = C₂H₅

15A; R = H

15B; R = CH₃

Several new iodoaminochromes have been described recently, including *N*-ethyl-7-iodonoradrenochrome (13A),⁶⁵ 7-iodoadrenochrome methyl ether (14A),⁶⁵ and 7-iodoadrenochrome ethyl ether (14B).⁶⁵ Improved procedures for the preparation of 7-iodonoradrenochrome (15A),^{70, 71} 7-iodo-2-methylnoradrenochrome (15B),⁷⁰ and 7-iodo-*N*-isopropylnoradrenochrome (13B)⁶⁵ have also been reported.

The aminochromes which have been obtained in the solid state and adequately characterized are listed in Table I.

⁶⁹ D. Richter and H. Blaschko, *J. Chem. Soc.* 601 (1937).

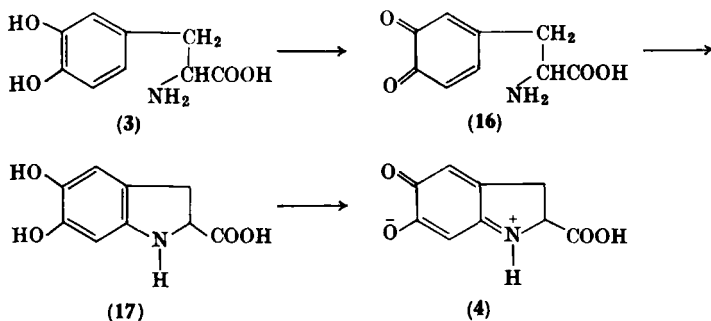
⁷⁰ R. A. Heacock, O. Hutzinger, B. D. Scott, J. W. Daly, and B. Witkop, *J. Am. Chem. Soc.* 85, 1825 (1963).

⁷¹ R. A. Heacock and B. D. Scott, *Experientia* 17, 347 (1961).

C. MECHANISM OF AMINOCHROME FORMATION FROM CATECHOLAMINES

The formation of aminochromes by the oxidation of catecholamines is usually a very rapid process. However, recent work has suggested that some of the highly reactive intermediate species, which are formed during the initial stages of the catecholamine oxidations and which have been largely overlooked in the past, may be of considerable physiological importance.

In his classical studies on melanin formation from DOPA (3), Raper proposed the following scheme for the formation of the red pigment now known to be the aminochrome "dopachrome" (4). The first stage involved the oxidation of the catechol nucleus of 3 to give the quinone "dopa-quinone" (16). The second stage was the non-oxidative intramolecular cyclization of 16 to "leuco-dopachrome" (17), which was in turn oxidized to dopachrome (4).^{72, 73} Since

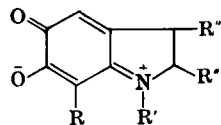


aminochrome formation normally occurs very rapidly at intermediate pH's, detection of intermediates, such as the uncyclized quinone 16, is a difficult problem. It is most probable that intramolecular cyclization of the 1-(β -aminoethyl)-3,4-benzoquinone (cf. 16) to form the corresponding aminochrome occurs by a nucleophilic attack on the electron-deficient quinone ring system by the amino group of the side chain. In strongly acid media, however, the ethylamine side chain of the *o*-quinone (cf. 16) will be protonated and consequently its nucleophilic character will be considerably diminished; in such cases the intermediate "open-chain quinone" will no longer readily undergo an intramolecular nucleophilic substitution, thus preventing aminochrome formation. In fact, oxidation of

⁷² H. S. Raper, *Biochem. J.* **21**, 89 (1927).

⁷³ W. L. Dulière and H. S. Raper, *Biochem. J.* **24**, 239 (1930).

TABLE I
AMINOCHROMES THAT HAVE BEEN PREPARED IN THE SOLID STATE



Aminochrome	R	R'	R''	R'''	Decomposition point, °C	Description
Noradrenochrome	H	H	H	OH	Not reported ^a	"Red rings on the side of the flask"
Adrenochrome ^b	H	CH ₃	H	OH	100–135 ^b	Deep red-violet needles
<i>N</i> -Ethylnoradrenochrome	H	C ₂ H ₅	H	OH	115 ^c	Dark red-violet prisms
<i>N</i> -Isopropylnoradrenochrome ^d	H	<i>i</i> -C ₃ H ₇	H	OH	123 ^c	Deep red-violet needles
Adrenochrome methyl ether	H	CH ₃	H	OCH ₃	83 ^c ; 86 ^e	Deep red microcrystalline solid
Adrenochrome ethyl ether	H	CH ₃	H	OC ₂ H ₅	70–72 ^c ; 81 ^e	Deep red microcrystalline solid
Epinochrome	H	CH ₃	H	H	78 ^f	Dark red rods
3-Acetoxyepinochrome	H	CH ₃	H	O-COCH ₃	90–91 ^g	Bright red crystalline solid
7-Iodonoradrenochrome ^h	I	H	H	OH	122–127 ⁱ	Dark violet needles ^j
7-Iodoadrenochrome ^{d, h}	I	CH ₃	H	OH	120 ^f	Violet-brown needles
7-Bromoadrenochrome ^{d, h}	Br	CH ₃	H	OH	90 ^f	Violet-brown platelets ^k
7-Iodo-2-methylnoradrenochrome ^h	I	H	CH ₃	OH	<i>ca.</i> 130 ⁱ	Violet-brown crystalline solid ^m
<i>N</i> -Ethyl-7-iodonoradrenochrome ^h	I	C ₂ H ₅	H	OH	134.5 ^c	Deep violet rods
7-Iodo- <i>N</i> -isopropylnoradrenochrome ^h	I	<i>i</i> -C ₃ H ₇	H	OH	105.5 ^c	Deep violet-brown needles ⁿ
7-Iodoadrenochrome methyl ether ^h	I	CH ₃	H	OCH ₃	85 ^c	Violet-brown needles
7-Iodoadrenochrome ethyl ether ^h	I	CH ₃	H	OC ₂ H ₅	88 ^c	Violet-brown needles

7-Iodonorepinochrome ^{d, h}	I	H	H	H	ca. 105°	Violet-brown microcrystalline solid
7-Iodoepinochrome ^h	I	CH ₃	H	H	85–87°; 120 ^f	Deep red needles ^g ; violet-brown crystalline solid ^f
2-Carbethoxy-7-iodonorepinochrome ^h	I	H	COOC ₂ H ₅	H	127°	Red needles
2-Carbethoxy-7-iodoepinochrome ^h	I	CH ₃	COOC ₂ H ₅	H	80°	"Red crystals"

^a P. Marquardt and E. Carl, *Naturwissenschaften* **39**, 210 (1952).

^b The preparation of crystalline adrenochrome has been described by several workers, and a number of different temperatures for the decomposition point of adrenochrome have been reported, however the majority fall between 100 and 135°. [See R. A. Heacock, *Chem. Rev.* **59**, 181 (1959) for references.]

^c R. A. Heacock and B. D. Scott, *Can. J. Chem.* **38**, 516 (1960).

^d For earlier references, see R. A. Heacock, *loc. cit.* (footnote "b").

^e The higher decomposition points were obtained when adrenochrome methyl and ethyl ethers were prepared by oxidation of the appropriate catecholamine in methanol with silver oxide. The solid aminochromes were then obtained as microcrystalline solids on addition of dry ether and cooling the resultant solution to –80°. The slightly less pure products were obtained when the oxidation was carried out in acetonitrile. [R. A. Heacock and B. D. Scott, *loc. cit.* (footnote "c")].

^f H. Sobotka and J. Austin, *J. Am. Chem. Soc.* **73**, 3077 (1951).

^g W. Schoeller, J. Jónás, and P. Marquardt, German Patent 866,039; *Chem. Abstr.* **52**, 16369 (1958).

^h It has recently been shown that the iodo-(or bromo-)aminochromes should be formulated as 7-iodo (or 7-bromo) derivatives [R. A. Heacock, O. Hutzinger, B. D. Scott, J. W. Daly, and B. Witkop, *J. Am. Chem. Soc.* **85**, 1825 (1963)]; consequently, all such compounds are described in this manner throughout this review.

ⁱ R. A. Heacock *et al.*, *loc. cit.* (footnote "h"); R. A. Heacock and B. D. Scott, *Experientia* **17**, 347 (1961).

^j This product was previously described as dark red (almost black) prisms; no melting point was reported [J. D. Bu'Lock and J. Harley-Mason, *J. Chem. Soc.* 712 (1951)].

^k This compound has also been described as deep red prisms; no melting point was reported. [J. Harley-Mason, *J. Chem. Soc.* 1276 (1950)].

^l R. A. Heacock *et al.*, *loc. cit.* (footnote "h").

^m This product was previously described as deep red needles; no melting point was reported [J. D. Bu'Lock and J. Harley-Mason, *loc. cit.* (footnote "e")].

ⁿ This product was previously described as reddish-brown needles; no melting point was reported [J. D. Bu'Lock and J. Harley-Mason, *loc. cit.* (footnote "e")].

^o R. A. Heacock and B. D. Scott, unpublished results (1962).

^p J. D. Bu'Lock and J. Harley-Mason, *J. Chem. Soc.* 2248 (1951).

^q J. Iwao and K. Tomino, *J. Pharm. Soc. Japan* **76**, 808 (1956).

catecholamines in strongly acid media (i.e., pH 1) gives yellowish-orange products, which can be reduced to the parent catecholamines. If these strongly acid solutions are neutralized they turn red irreversibly, presumably due to cyclization of some of the open-chain quinone molecules.⁷⁴⁻⁷⁶

More definite evidence for the transient existence of the uncyclized 1-(β -aminoethyl)-3,4-benzoquinones has been obtained recently by Kodja and Bouchilloux,^{77, 78} who noted that a transient yellow color (λ_{\max} ca. 385 m μ) was occasionally observed during the enzymic oxidations of catecholamines (particularly in unbuffered systems at low temperatures). This phenomenon was probably due to the formation of the transient *o*-quinones. (The absorption maximum of *o*-benzoquinone, the effective chromophore of the open-chain quinones, is known to occur at ca. 390 m μ .⁷⁹) An absorption maximum at 390 m μ is characteristic of the formation of the dopa-quinone chromophore during oxidation of small C-terminal tyrosine peptides in the presence of tyrosinase.^{37, 48} Similar spectroscopic features were observed when the oxidations were carried out with lead dioxide in sulfuric acid solutions (pH \gg 1). If the initial oxidation was carried out for a short period of time, it was possible to regenerate the original catecholamines by reduction (e.g. with sodium bisulfite, potassium iodide, and zinc powder) and to show that the 385 m μ peak disappeared.^{77, 78} Kodja and Bouchilloux were also able to identify 2,4-dinitrophenylhydrazones of several of the intermediate non-cyclized quinones by paper chromatography and spectroscopy (λ_{\max} in weakly acid solution ca. 350 m μ with a shoulder at ca. 410 m μ).^{77, 78}

A considerable amount of evidence has accumulated recently for the transient existence of free-radical intermediates in systems containing oxidizing catecholamines. Walaas and Walaas and their co-workers have shown that the interaction of catecholamines with cupric ion (either bound, as in ceruloplasmin, or as the free ion, cf. ref. 80) results initially in reduction of the copper atom to the

⁷⁴ J. D. Bu'Lock and J. Harley-Mason, *J. Chem. Soc.* 712 (1951).

⁷⁵ M. Rangier, *Compt. Rend.* **220**, 246 (1945).

⁷⁶ J. Ruiz-Gijón, *Nature* **166**, 831 (1950).

⁷⁷ A. Kodja and S. Bouchilloux, *Compt. Rend. Soc. Biol.* **153**, 1407 (1959).

⁷⁸ A. Kodja and S. Bouchilloux, *Biochim. Biophys. Acta* **41**, 345 (1960).

⁷⁹ H. S. Mason, *J. Biol. Chem.* **181**, 803 (1949).

⁸⁰ L. Broman, B. C. Malmstrom, R. Aasa, and T. Vänngård, *J. Mol. Biol.* **5**, 301 (1962).

cuprous state and in the formation of an "activated" catecholamine molecule,^{14, 23, 24} which was described as being in a free-radical or a highly active quinonoid form.^{22, 24} In the presence of oxygen this intermediate readily undergoes further oxidation to the corresponding aminochrome. A similar "activated" catecholamine molecule was obtained by photoactivation with ultraviolet light.⁶¹

These workers also showed that reduced diphosphopyridine nucleotide (DPN) and triphosphopyridine nucleotide (TPN) could be oxidized by systems containing ceruloplasmin and suitable substrates (including adrenaline and noradrenaline).²² The oxidation of the DPN or TPN was brought about by some highly active intermediate species and not by adrenochrome or noradrenochrome (i.e., the final oxidation products of these catecholamines in the presence of ceruloplasmin).²² *p*-Phenylenediamine and *N,N*-dimethyl-*p*-phenylenediamine are also suitable substrates for these coupled oxidation systems. In the latter case, the formation of the stable free radical known as "Wurster's Red" provided definite evidence for free radical formation in systems of this type.²² Transitory free radicals were reported to be formed from catechols when they were irradiated or acted upon by a polyphenoloxidase.⁸¹ The oxidation of reduced phosphopyridine nucleotides by a catechol-polyphenoloxidase system, presumably by a free-radical mechanism, has also been described.^{82, 83} Direct evidence for the formation of free radicals during the autoxidation of DOPA has been obtained by E.S.R. spectroscopy.⁸⁴ Finally, there is the kinetic evidence of Sokoloski and Higuchi for free radical formation during the autoxidation of adrenaline solutions.¹⁰

The interaction of unspecified "catecholamine oxidation products" with certain sulfhydryl compounds, including cysteine, glutathione, and coenzyme A, has been studied by Roston.⁸⁵⁻⁸⁸ It appeared that

⁸¹ A. M. LeClerc, J. Mondy, P. Douzou, and S. Lissitsky, *Biochim. Biophys. Acta* **32**, 499 (1959).

⁸² D. Kertesz and O. Azzopardi, *Compt. Rend. Soc. Biol.* **154**, 270 (1960).

⁸³ D. Kertesz and O. Azzopardi, *Bull. Soc. Chim. Biol.* **42**, 945 (1960).

⁸⁴ J. E. Wertz, D. C. Reitz, and F. Dravnieks, in "Free Radicals in Biological Systems, Proceedings of a Symposium Held at Stanford University, March, 1960" (M. S. Blois, Jr., H. W. Brown, R. M. Lemmon, R. O. Lindblom, and M. Weissbluth, eds.), p. 183. Academic Press, New York, 1961.

⁸⁵ S. Roston, *Arch. Biochem. Biophys.* **85**, 74 (1959).

⁸⁶ S. Roston, *J. Biol. Chem.* **235**, 1002 (1960).

⁸⁷ S. Roston, *J. Biol. Chem.* **235**, 3315 (1960).

⁸⁸ S. Roston, *Nature* **197**, 75 (1963).

intermediate oxidation products of the catecholamines reacted with the thiols, thus reducing the ultimate conversion into the corresponding aminochromes. Bouchilloux and Kodja reported that the oxidation of tyrosine or DOPA in the presence of glutathione, resulted in the formation of a product probably derived from the interaction of the initially formed dopa-quinone and glutathione. This compound, which was relatively stable, was described as a 3,4-dihydroxyphenylalanine derivative with the glutathione residue attached to the 6-position by a sulfide linkage.⁸⁹

Harrison has recently followed the early stages of adrenaline and noradrenaline oxidations under "physiological conditions," with respect to concentration and pH, fluorimetrically.^{90, 91} The oxidations were carried out with the following oxidizing reagents and catalysts: (i) potassium ferricyanide, (ii) Cu^{++} ions (free and bound, as in ceruloplasmin and tyrosinase), (iii) Fe^{+++} ions, and (iv) manganese dioxide. In the case of oxidation by ferricyanide, the first step (detected by the loss of the native catecholamine fluorescence in the ultraviolet region) occurred very rapidly for both adrenaline and noradrenaline (ca. 30 sec at pH 6.0–7.0 and ca. 90 sec at pH 5.5). The second step was the formation of oxidation products of the catecholamines, which did not fluoresce under the existing reaction conditions but were readily converted into fluorescent derivatives by the action of ascorbic acid. (The fluorescence characteristics of the products obtained from adrenaline in this manner were different from those of the corresponding noradrenaline derivatives.) The pH 6-oxidation, ascorbic acid-treated products of both bases were, in turn, converted into products with fluorescence characteristics of the 5,6-dihydroxy-indoxyls on treatment with alkali.⁹⁰

When adrenaline was oxidized in the presence of Cu^{++} ions, the loss of the native catecholamine fluorescence was again detected, but in this case the initial oxidation products were also fluorescent. Addition of ascorbic acid did not increase the fluorescence. However, addition of ferricyanide ions destroyed the fluorescence, but it could be regenerated by the addition of ascorbic acid. Noradrenaline behaved somewhat differently in that the initial oxidation product had little fluorescence, probably due to the quenching effect of the Cu^{++} ions, since reduction of the Cu^{++} ion concentration increased

⁸⁹ S. Bouchilloux and A. Kodja, *Bull. Soc. Chim. Biol.* **42**, 1045 (1960).

⁹⁰ W. H. Harrison, *Arch. Biochem. Biophys.* **101**, 116 (1963).

⁹¹ W. H. Harrison, *Biochim. Biophys. Acta* **70**, 705 (1963).

the fluorescence and the addition of EDTA, in sufficient amount to complex the Cu^{++} ions used, led to the development of fluorescence of equal intensity to that obtained from adrenaline. Reversible loss and regeneration of fluorescence was observed by the alternative additions of equivalent amounts of Cu^{++} and EDTA. Oxidations in the presence of Fe^{+++} ions and with manganese dioxide appeared to follow basically similar courses, but the products in the latter case had different fluorescence characteristics from those obtained with other oxidants.⁹⁰

The possibility that the apparently different fluorescence characteristics observed for the various intermediates obtained from a given catecholamine may be due to physical effects and that the products may, in fact, all be the same, cannot be entirely ruled out at the moment. Harrison suggests that they are not *o*-quinones since such compounds do not fluoresce (cf. ref. 92). These fluorescent products were not detectable at higher concentration, possibly because of concentration quenching.⁹⁰ In a later publication Harrison suggests that the intense fluorescence obtained upon addition of the optimum amount of ascorbic acid to the initial noradrenaline oxidation product (obtained with ferricyanide at pH 6.0) might be used to detect this catecholamine, since negligible fluorescence is obtained from adrenaline under the same conditions.⁹¹ It is interesting that this particular fluorescent compound was not converted into any products exhibiting the expected noradrenolutin fluorescence characteristics on the addition of alkali.⁹¹ Although it is difficult to be exactly sure of what all these fluorescence measurements mean at present, this approach to the problem warrants further study.

In summary, it would appear that the oxidation of a catecholamine probably first involves the formation of a semi-quinone radical (this can be brought about by an one-electron transfer, e.g. from Cu^{++} ions,¹⁴ or by photoactivation⁶¹) which rapidly undergoes further oxidation (e.g. with atmospheric oxygen) to an intermediate "open-chain quinone" (such as adrenaline-quinone) and then cyclizes by an oxidative nucleophilic intramolecular substitution to the aminochrome molecule. Whilst the initial formation of a leucoaminochrome by non-oxidative cyclization of the intermediate "open-chain quinone" in some cases cannot be entirely excluded at the moment (cf. Raper's original scheme for aminochrome formation⁷²), the

⁹² S. Udenfriend, "Fluorescence Assay in Biology and Medicine," p. 139. Academic Press, New York, 1962.

importance of such a step is questionable. The 3-hydroxy-leuco-aminochromes are known to lose water very readily to form 5,6-dihydroxyindoles (e.g. the formation of 5,6-dihydroxy-*N*-methylin-dole on reduction of adrenochrome; see Section IV, C). In such cases, 5,6-dihydroxyindole formation would be expected to occur to some extent, although this would depend on the relative rates of the dehydration and reoxidation reactions of the leuco-aminochrome, particularly since such a compound would presumably be formed in the presence of an excess of the oxidizing reagent.

It appears that the intermediates formed from different catecholamines are of different stability. The intermediate open-chain quinones derived from catecholamines with a primary amino group in the side chain do not appear to undergo intramolecular cyclization very readily and consequently would be able to take part in competing reactions; this would account for the fact that in general it is difficult to obtain efficient conversions of such catecholamines (e.g. noradrenaline) into the corresponding aminochromes. This factor is important in catecholamine assay procedures (see Section V, E) and probably explains the wide variability in the apparent efficiency of the noradrenaline oxidation procedures used (as measured by the intensity of the fluorescence of the noradrenolutin obtained by the particular method). The fact that noradrenaline-quinone is relatively more stable than adrenaline-quinone accounts for the formation of entirely different types of fluorescent products from adrenaline and noradrenaline, respectively, in the Weil-Malherbe assay procedure for catecholamines (see Sections IV, H and V, E, 5).

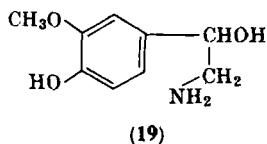
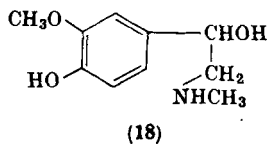
It has often been claimed that the poor conversion of noradrenaline into noradrenochrome normally observed was due to the instability of noradrenochrome. It now appears that noradrenochrome, once formed, is relatively stable (see Section IV, B, 5); the low yields of noradrenochrome usually obtained probably result from the participation of the longer-lived intermediate oxidation products in competing reactions.

D. OTHER ROUTES TO THE AMINOCROMES

1. Oxidation of β -(4-Hydroxy-3-methoxyphenyl)ethylamines

The β -(4-hydroxy-3-methoxyphenyl)ethylamines [i.e. the catecholamine *O*³-methyl ethers, metanephrine (18) and normetanephrine (19)] are known to be among the major *in vivo* metabolites of

adrenaline and noradrenaline (cf. refs. 93, 94). Recently chemical assay procedures for these compounds, which are basically similar to the well-known "trihydroxyindole" method (see Section V, E, 2) for adrenaline and noradrenaline, have been described. Metanephrine (18) and normetanephrine (19) give products on oxidation with iodine



at neutral pH that, on treatment with alkaline ascorbic acid^{95, 96} (or alkaline sodium sulfite^{97, 98}), give derivatives with fluorescence characteristics very similar to those observed for adrenaline and noradrenaline, respectively, under similar conditions.⁹⁵⁻⁹⁸

Presumably the fluorescent products are adrenolutin and noradrenolutin; consequently, the corresponding aminochromes must have been present at the previous stage. It would appear, therefore, that the 3-methoxy group is first demethylated and that the oxidation follows the usual course, producing the 7-iodoaminochromes which subsequently undergo the normal rearrangement and deiodination reactions to give the fluorescent "lutins." The oxidation of 18 and 19 with iodine requires a more alkaline pH (i.e. 6.5-7.0) than is usual for oxidation of the simple catecholamines. Bertler *et al.* claim that potassium ferricyanide does not oxidize these compounds under the same conditions that it oxidizes the catecholamines,⁹⁵ and ferricyanide has been used to destroy preferentially the simple catecholamines in a differential assay procedure.^{97, 98} Weil-Malherbe and Smith, however, claim that 18 can be oxidized, presumably to adrenochrome, with the zinc-ferricyanide system (see Section V, E, 2), using a much higher concentration of zinc ions than is normally used.^{99, 100} However, these authors could not oxidize 19 with this

⁹³ J. Axelrod, *Pharmacol. Rev.* **11**, 402 (1959).

⁹⁴ J. Axelrod, *Physiol. Rev.* **39**, 751 (1960).

⁹⁵ A. Bertler, A. Carlsson, and E. Rosengren, *Clin. Chim. Acta* **4**, 456 (1959).

⁹⁶ A. Randrup, *Clin. Chim. Acta* **6**, 584 (1961).

⁹⁷ A. Carlsson and M. Lindqvist, *Acta Physiol. Scand.* **54**, 83 (1962).

⁹⁸ J. Häggendal, *Acta Physiol. Scand.* **56**, 258 (1962).

⁹⁹ E. R. B. Smith and H. Weil-Malherbe, *J. Lab. Clin. Med.* **60**, 212 (1962).

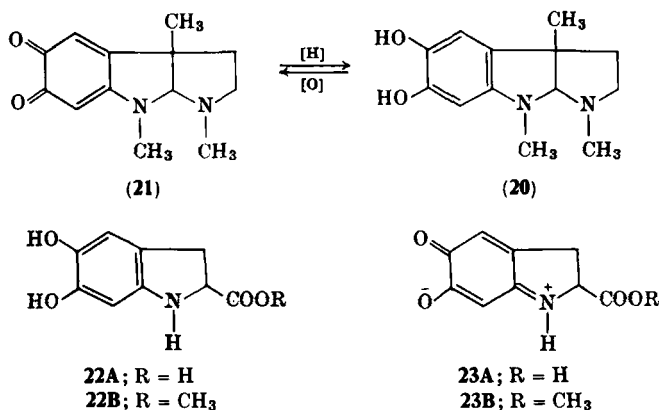
¹⁰⁰ H. Weil-Malherbe and E. R. B. Smith, *J. Neuropsychiat.* **4**, 113 (1962).

reagent; they employed the iodine oxidation procedure (at mildly alkaline pH) for its determination.^{99, 100}

The mechanisms of these interesting oxidations require further study, and attempts should be made to isolate the intermediate aminochromes (or a simple derivative, such as the semicarbazone). However, it is difficult to escape the conclusion that aminochromes can be readily obtained by the oxidation of compounds such as metanephrine and normetanephrine.

2. Oxidation of 5,6-Dihydroxyindolines

No examples of true leuco derivatives of the most common aminochromes with a 3-hydroxyl group (i.e. 3,5,6-trihydroxyindolines) have been isolated. However, such derivatives have been obtained from some aminochromes (or closely related compounds) without a 3-hydroxyl group, and these leuco compounds can be very easily reoxidized to the corresponding aminochromes. One of the best known examples of a reaction of this type is the very facile oxidation of leuco-rubreserine (**20**) to rubreserine (**21**).^{101, 102}



5,6-Dihydroxyindoline-2-carboxylic acid (**22A**) (i.e. "leucodopa-chrome"), which can be obtained by the anaerobic alkaline degradation of betanidin¹⁰³ (i.e. the aglycone of the beet pigment betanin;

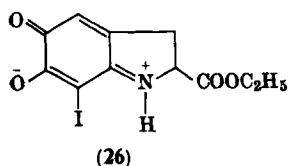
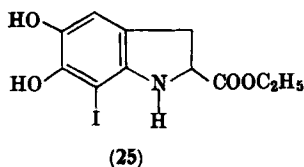
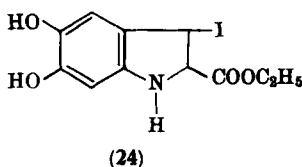
¹⁰¹ A. H. Salway, *J. Chem. Soc.* **101**, 978 (1912).

¹⁰² S. Ellis, *J. Pharmacol. Exp. Therap.* **79**, 364 (1943).

¹⁰³ H. Wyler and A. S. Dreiding, *Helv. Chim. Acta* **45**, 638 (1962).

see Section VI, B, 1), readily oxidizes in air to dopachrome (23A). Analogously, methyl 5,6-dihydroxyindoline-2-carboxylate (22B) is readily autoxidized in air to the methyl ester of dopachrome (23B).¹⁰³

A substance described as ethyl 2,3-dihydro-5,6-dihydroxy-3-iodoindole-2-carboxylate (24), but which is probably the corresponding 7-iodo compound (25) (see Section IV, E), has been prepared by reduction of the ethyl ester of iododopachrome (26), and this is readily reoxidized in air to the corresponding aminochrome (shown spectroscopically).¹⁰⁴



III. Physical Properties of the Aminochromes

A. GENERAL COMMENTS

The non-halogenated aminochromes are all deep red to red-violet crystalline solids, readily soluble in water and methanol giving deep red solutions; their solubility in the lower aliphatic alcohols rapidly decreases with increasing molecular weight of the alcohol. These compounds are slightly soluble in polar solvents like acetonitrile, acetone, and nitromethane, but are virtually insoluble in non-polar solvents, such as benzene. The iodo- or bromo-aminochromes are usually deep violet-brown crystalline solids, only slightly soluble in polar solvents, giving violet-colored solutions. Most aminochromes do not melt, but decompose without melting on heating. The decomposition point (or range) can be readily observed on a hot stage polarizing microscope (the aminochrome *O*³-alkyl ethers, however, appear to melt normally before decomposing⁶⁵). When heated

¹⁰⁴ J. D. Bu'Lock and J. Harley-Mason, *J. Chem. Soc.* 2248 (1951).

TABLE II
ABSORPTION SPECTRA OF SOME AMINOCHROMES^{a, b}

Aminochrome	Solvent ^c	Absorption maxima, mμ ^b	Absorption minima, mμ ^b
Noradrenochrome ^{a, d-g}	W	205-215, 281-310, 484-490	253-258, 365-370
Adrenochrome ^{a, d, e, g-j}	M	296, 470	261, 374
	W	220, 301, 480-490	260-262, 361-365
<i>N</i> -Ethylnoradrenochrome ^{g, k}	M	301, 472	262, 380
	W	303, 490	261, 368
<i>N</i> -Isopropylnoradrenochrome ^{d, g, k}	M	301, 485	263, 364
	W	220, 300-303, 485-495	261, 366
2-Methyladrenochrome ^g	W	301, 487	260, 365
<i>N</i> -Ethyl-2-methylnoradrenochrome ^g	W	303, 490	260, 367
Adrenochrome methyl ether ^k	M	297, 480	270, 372
	W	302, 492	262, 374
Adrenochrome ethyl ether ^k	M	297, 478	272, 377
	W	302, 488	262, 370
Epinochrome ^{d, g, h, k}	E	205, 305, 470	—
	W	303-308, 470-480	257-258, 364-369
Dopachrome ^{e, l}	W	215, 304-305, 473-475	257, 375
Norepinochrome ^e	W	213, 298, 473	254, 365
7-Iodonoradrenochrome ^{e, m, n}	W	223, 293, 508-510	263-269, 345-382
7-Iodoadrenochrome ^{a, e, h, k, m, o}	M	233, 302, 528	268, 385
	W	231-233, 301-304, 525-535	268, 385
	E	234, 302, 530	268, 385
7-Bromadrenochrome ^{m, h}	E	227, 306, 520	—
7-Iodo-2-methylnoradrenochrome ^{m, n}	M	523	400
	W	224, 297, 523	265, 380

<i>N</i> -Ethyl-7-iodonoradrenochrome ^{k, m}	M	232, 303, 525	270, 400
	W	232, 303, 535	268, 386
7-Iodo- <i>N</i> -isopropylnoradrenochrome ^{k, m}	M	233, 302, 528	268, 380
	W	232, 306, 535	268, 390
7-Ioadrenochrome methyl ether ^{k, m}	M	233, 300, 530	268, 390
	W	233, 302, 535	267, 388
7-Ioadrenochrome ethyl ether ^{k, m}	M	222, 300, 508	265, 375
	W	223, 302, 505	264, 372
7-Iodonorepinochrome ^{m, n}	W	298, 500	260, 368
7-Iodoepinochrome ^{m, n}	M	510	398
	E	217, 305, 510	—
2-Carbethoxy-7-iodonorepinochrome ^{m, p}	E	298, 490	—

^a For earlier references, see (i) R. A. Heacock, *Chem. Rev.* **59**, 181 (1959), and (ii) H. Sobotka, N. Barsel, and J. D. Chanley, *Fortschr. Chem. Org. Naturstoffe* **14**, 217 (1957).

^b Where several values for a particular maximum or minimum have been given in the literature, the range in which the majority of these values fall is reported here.

^c W = water, M = methanol, and E = ethanol.

^d C. Beaudet, *Experientia* **7**, 291 (1951).

^e S. Bouchilloux, *Compt. Rend. Soc. Biol.* **153**, 1818 (1959).

^f S. Bouchilloux and A. Kodja, *Bull. Soc. Chim. France* **42**, 65 (1960).

^g R. A. Heacock and G. L. Mattok, *Can. J. Chem.* **41**, 139 (1963).

^h H. Sobotka and J. Austin, *J. Am. Chem. Soc.* **73**, 3077 (1951).

ⁱ R. A. Heacock, C. Nerenberg and A. N. Payza, *Can., J. Chem.* **36**, 853 (1958).

^j A. Feldstein, *Science* **128**, 28 (1958).

^k R. A. Heacock and B. D. Scott, *Can. J. Chem.* **38**, 516 (1960).

^l H. S. Mason, *J. Biol. Chem.* **172**, 83 (1947) (spectrum determined in aqueous buffer pH 5.6).

^m It has recently been shown that the iodo-(or bromo-)aminochromes should be formulated as 7-iodo (or 7-bromo) derivatives [R. A. Heacock, O. Hutzinger, B. D. Scott, J. W. Daly and B. Witkop, *J. Am. Chem. Soc.* **85**, 1825 (1963)]; consequently, all such compounds are described in this manner throughout this review.

ⁿ G. L. Mattok, D. L. Wilson, B. D. Scott, and R. A. Heacock, unpublished results (1960-1964).

^o R. A. Heacock and B. D. Scott, *Can. J. Chem.* **38**, 508 (1960).

^p J. D. Bu'Lock and J. Harley-Mason, *J. Chem. Soc.* 2248 (1951).

in a free flame the aminochromes decompose vigorously leaving a hard coke-like residue.

Owing to the intense color of solutions of the aminochromes, measurement of their optical rotation presents some difficulties. However, the rotation of adrenochrome, freshly prepared from L-adrenaline, is reported to be $[\alpha]_{630}^{25} = ca. +150^\circ$.² The sign of the rotation changes during the oxidation; this fact is in agreement with the observed sign of rotation of adrenochrome monosemicarbazone prepared from L-adrenaline.¹⁰⁵

B. SPECTROSCOPY

1. Ultraviolet and Visible Spectroscopy

In general the ultraviolet and visible absorption spectra of all aminochromes measured in aqueous or methanolic solution show two distinct maxima in the ultraviolet region, one in the 200–230 m μ region and the other at *ca.* 300 m μ . The non-halogenated aminochromes are also characterized by a broad, flat maximum in the 470–490 m μ region, whilst the iodo- and bromo-aminochromes show a similar maximum at somewhat longer wavelengths (i.e. 520–535 m μ) (see refs. 2 and 3 for lists of early references). The ultraviolet and visible absorption spectral characteristics reported recently for several aminochromes are given in Table II. In general the absorption maximum in the visible region is observed at slightly longer wavelengths in aqueous solution than in methanol.⁶⁵ In the series noradrenochrome (λ_{\max} 484 m μ), adrenochrome (λ_{\max} 487 m μ), *N*-ethylnoradrenochrome (λ_{\max} 490 m μ), and *N*-isopropylnoradrenochrome (λ_{\max} 495 m μ), a progressive shift in the visible absorption (of aqueous solutions) towards lower frequencies is noted with increasing size of the *N*-alkyl group.^{65, 106}

The aminochromes form yellow solutions in strongly acid media and the long-wavelength absorption maximum is shifted to *ca.* 380–400 m μ .^{3, 77, 78, 107} Since the aminochromes decompose rapidly under these conditions, it is difficult to measure their spectra in strongly acid media with any great accuracy.⁷⁸

¹⁰⁵ C. Beaudet, F. Debot, H. Lambot, and J. Toussaint, *Experientia* **7**, 291 (1951).

¹⁰⁶ R. A. Heacock and G. L. Mattok, *Can. J. Chem.* **41**, 139 (1963).

¹⁰⁷ J. D. Bu'Lock, *J. Chem. Soc.* 52 (1961).

2. *Infrared Spectroscopy*

The infrared spectra of adrenochrome, adrenochrome methyl ether, and 7-iodoadrenochrome in the solid state (Nujol mulls) have

TABLE III
INFRARED SPECTRA OF SOME AMINOCHROMES^{a, b}

Aminochrome	4000-2500 cm ⁻¹	1800-1500 cm ⁻¹
Adrenochrome ^c	3295 (m)	1682 (m-s) 1672 (m, sh) 1622 (m) 1575 (s)
<i>N</i> -Ethylnoradrenochrome ^d	3275 (m)	1668 (m-s) 1655 (m, sh) 1580 (s)
Adrenochrome methyl ether ^d	—	1678 (m-s) 1637 (m, sh) 1630 (m, sh) 1600 (s)
7-Iodoadrenochrome ^{c, e}	3420 (m)	1674 (m-s) 1657 (m, sh) 1612 (m) 1562 (s)
7-Iodo- <i>N</i> -isopropylnoradrenochrome ^{d, e}	3410 (m)	1685 (m-s) 1675 (m, sh) 1595 (m, sh) 1540 (s)
7-Bromoadrenochrome ^{d, e}	3260 (m)	1670 (m-s) 1655 (m, sh) 1620 (m) 1553 (s)

^a The spectra were recorded as Nujol mulls on a Perkin-Elmer model 21 spectrophotometer (with sodium chloride optics).

^b The main absorption peaks in the "O—H stretching" and "carbonyl" regions only are reported; s = strong, m = medium, sh = shoulder.

^c Data taken from R. A. Heacock and M. E. Mahon, *Can. J. Chem.* **36**, 1550 (1958).

^d R. A. Heacock, unpublished work (1960-1964).

^e It has recently been shown that the iodo-(or bromo-)aminochromes should be formulated as 7-iodo (or 7-bromo) derivatives [R. A. Heacock, O. Hutzinger, B. D. Scott, J. W. Daly, and B. Witkop, *J. Am. Chem. Soc.* **85**, 1825 (1963)]; consequently, all such compounds are described in this manner throughout this review.

been reported.¹⁰⁸⁻¹¹⁰ The main absorption peaks of several other aminochromes which have been recorded by the author¹¹¹ are given in Table III. The aminochromes with a 3-hydroxyl group show the O—H stretching peak between 3250–3420 cm^{-1} . The infrared spectra of the aminochromes all show a somewhat complex absorption pattern in the “carbonyl” region; one characteristic feature of this area is the intense absorption usually observed at 1550–1600 cm^{-1} , probably due to the ionized carbonyl group at C-6.

3. Fluorescence and Nuclear Magnetic Resonance Spectroscopy

Freshly prepared solutions of pure samples of the aminochromes should not exhibit any fluorescence. However, the ease with which they are converted into highly fluorescent 5,6-dihydroxyindoxyls (see Section IV, B) and 5,6-dihydroxyindoles (see Sections IV, B and IV, C) might lead to some confusion, since solutions of aminochromes contaminated with such compounds would undoubtedly fluoresce (cf. ref. 112).

Preliminary attempts to obtain the n.m.r. spectra of several aminochromes were unsuccessful owing to the limited solubility of these compounds in suitable solvents.⁷⁰

C. PAPER CHROMATOGRAPHY

In view of the very high reactivity of the aminochromes in solution, paper chromatographic studies with these compounds present a number of difficulties. For instance, the ease with which the aminochromes may interact with the solvent system being used, or with impurities in the paper, must be taken into consideration. One of the solvent systems which has been extensively employed for the paper chromatographic separation of aromatic compounds (i.e. an isopropanol-ammonia-water mixture) is quite unsatisfactory in this case, since, in the experience of the author, total decomposition of the aminochromes in basic solvents invariably occurs very rapidly.⁶⁴ This is not surprising in view of the known sensitivity of the amino-

¹⁰⁸ R. A. Heacock and M. E. Mahon, *Can. J. Chem.* **36**, 1550 (1958).

¹⁰⁹ R. A. Heacock and B. D. Scott, *Can. J. Chem.* **38**, 508 (1960).

¹¹⁰ R. A. Heacock, *Chem. Ind. (London)* 752 (1959).

¹¹¹ R. A. Heacock, unpublished data (1960–1964).

¹¹² R. A. Heacock, G. L. Mattok, and D. L. Wilson, *Can. J. Biochem. Physiol.* **41**, 1721 (1963).

chromes to bases in general and the reported rapid interaction of adrenochrome with ammonia.¹¹³ However, R_f values have been reported for adrenochrome in isopropanol-aqueous ammonia and butanol-aqueous ammonia systems, although it was noted that the product "streaked" in these systems.¹¹⁴ An R_f value for adrenochrome in another basic system, i.e. methyl ethyl ketone-diethylamine-water, has also been quoted.¹¹⁵ Slow decomposition of the aminochromes has also been reported to occur in *n*-butanol-acetic acid-water systems,⁶⁴ although a definite R_f value for adrenochrome in a solvent system of this nature can apparently be obtained if the running time is kept comparatively short (i.e. > 3 hours).¹¹⁶ Decomposition of adrenochrome (i.e. 3 spots observed on chromatograms) during chromatography with *n*-butanol-acetic acid-water systems has been described by Szepesy,¹¹⁷ and Bouchilloux and Kodja also observed that the aminochromes decompose when chromatographed in *n*-butanol-acetic acid-water systems.^{118, 119} Reio, however, has recorded R_f values for adrenochrome in three formic acid-containing solvent mixtures.¹¹⁵

The most satisfactory solvent systems described so far for paper chromatography of the aminochromes are either double-distilled water or 2% aqueous acetic acid.^{64, 65, 89, 116, 118-123} The use of acid-washed chromatographic paper considerably retards decomposition of the aminochromes. The acid washing ensures removal of metal ions which might catalyze the decomposition^{64, 112} and removes residual traces of sulfites and bisulfites from the paper, which form addition complexes with the aminochromes¹²³ (see Section IV, F). There is a marked increase in the tendency of adrenochrome to rearrange to adrenolutin (see Section IV, B, 2) in the lower aliphatic alcoholic

¹¹³ T. Pavolini, F. Gambarin, and A. S. Godenigo, *Gazz. Chim. Ital.* **81**, 527 (1951).

¹¹⁴ E. G. McGeer, M. C. Robertson, and P. L. McGeer, *Can. J. Biochem. Physiol.* **39**, 605 (1961).

¹¹⁵ L. Reio, *J. Chromatog.* **4**, 458 (1960).

¹¹⁶ J. J. Noval, A. Sohler, S. P. Stackhouse, and A. C. Bryan, *Biochem. Pharmacol.* **11**, 467 (1962).

¹¹⁷ A. Szepesy, *Gyógyszerészet* **6**, 267 (1962); *Chem. Abstr.* **57**, 15245 (1962).

¹¹⁸ S. Bouchilloux and A. Kodja, *Bull. Soc. Chim. Biol.* **42**, 65 (1960).

¹¹⁹ S. Bouchilloux, *Compt. Rend. Soc. Biol.* **153**, 1818 (1959).

¹²⁰ S. Bouchilloux and A. Kodja, *Compt. Rend.* **247**, 2484 (1958).

¹²¹ S. Bouchilloux, *Compt. Rend. Soc. Biol.* **155**, 1325 (1961).

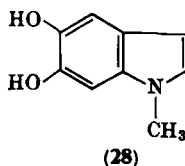
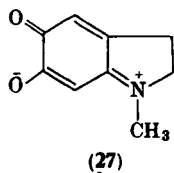
¹²² S. Bouchilloux and A. Kodja, *Compt. Rend.* **251**, 1920 (1960).

¹²³ S. Bouchilloux, *Compt. Rend. Soc. Biol.* **153**, 642 (1959).

solvents¹¹²; consequently solvent mixtures including such alcohols should be avoided wherever possible. Adrenochrome can be readily separated paper-chromatographically from several of its common derivatives, such as adrenochrome monosemicarbazone, adrenolutin and 5,6-dihydroxy-*N*-methylindole, with the upper phase of a chloroform-methanol-water (10:10:6) system on acetylated paper.¹²⁴ Adrenochrome appears to be moderately stable in this system.¹²⁴

The aminochromes are highly colored, consequently it is not usually necessary to use a spray reagent to locate the spot. The red color of such spots, however, rapidly fades on drying of the developed chromatograms.⁶⁴ The resulting pale yellow-brown spots then exhibit either (i) an intense yellow-green fluorescence⁶⁴ due to the corresponding 5,6-dihydroxyindoxyl, if the original aminochrome had a 3-hydroxyl group, or (ii) the weaker blue fluorescence of a 5,6-dihydroxyindole, if the aminochrome had no substituent in the 3-position (see Section IV, B).^{65, 118} These processes (i.e. rearrangement) can be speeded up by spraying the chromatograms with 10% zinc acetate solution. This reagent also readily distinguishes the aminochromes with a 3-alkoxyl group from those with a 3-hydroxyl group, the ethers merely giving a distinctive dark blue non-fluorescent pigment.^{65, 106, 110} Definite color reactions can be obtained from aminochrome spots by spraying the papers with Ehrlich's reagent,^{64, 65} *p*-dimethylaminocinnamaldehyde,⁶⁵ diazotized *p*-nitroaniline,^{64, 65} or ferric chloride-potassium ferricyanide.⁶⁴ Spraying the developed chromatograms with aqueous sodium bisulfite converts the aminochrome spot into a stable sodium bisulfite addition product which exhibits a yellow fluorescence in ultraviolet light¹²³ (see Section IV, F).

In practice, it was impossible to prevent the partial rearrangement of aminochromes without 3-hydroxyl or 3-alkoxyl groups during paper chromatography, even in the most innocuous solvents. All attempts to chromatograph epinochrome (27) with 2% acetic acid as running solvent gave, in addition to the red epinochrome spot



¹²⁴ R. A. Heacock and M. E. Mahon, *J. Chromatog.* **6**, 91 (1961).

(R_f ca. 0.8), an intense spot due to its rearrangement product [i.e. 5,6-dihydroxy-*N*-methylindole (28)] and an unknown Ehrlich-positive spot (R_f ca. 0.25).⁶⁵

The R_f values that have been reported recently for some aminochromes in several solvent systems are given in Table IV.

TABLE IV
PAPER CHROMATOGRAPHIC DATA ON SOME AMINOCHROMES

Aminochrome	R_f values ^{a, b}	
	Solvent 1 ^c	Solvent 2 ^c
Norepinochrome	70 ^{d, e}	—
Noradrenochrome	75 ^{d, e} , 77 ^{d, f}	—
Adrenochrome	68 ^{d, f} , 80 ^{d, g}	78 ^{d, h} , 82 ^{d, g} , 92 ^{d, f}
<i>N</i> -Ethylnoradrenochrome	—	79 ^{d, h}
<i>N</i> -Isopropylnoradrenochrome	—	77 ^{d, h}
Dopachrome	92 ^{d, e}	—
Adrenochrome methyl ether	—	81 ^{d, h}
Adrenochrome ethyl ether	—	82 ^{d, h}
Epinochrome	—	ca. 80 ^{d, h, k}
7-Iodonoradrenochrome ^l	66 ^{d, f}	—
7-Iodoadrenochrome ^l	82 ^{d, f}	—

^a R_f value $\times 100$.

^b Water and 2% aqueous acetic acid have proved to be the most successful solvent systems so far used for paper chromatography of the aminochromes (see text).

^c Solvent 1 = distilled water; solvent 2 = 2% aqueous acetic acid.

^d Acid-washed Whatman No. 1 paper.

^e S. Bouchilloux and A. Kodja, *Bull. Soc. Chim. Biol.* **42**, 65 (1960).

^f S. Bouchilloux, *Compt. Rend. Soc. Biol.* **153**, 1818 (1959).

^g R. A. Heacock, C. Nerenberg and A. N. Payza, *Can. J. Chem.* **36**, 853 (1958).

^h R. A. Heacock and B. D. Scott, *Can. J. Chem.* **38**, 516 (1960).

ⁱ J. J. Noval, A. Sohler, S. P. Stackhouse and A. C. Bryan, *Biochem. Pharmacol.* **11**, 467 (1962).

^j Whatman No. 54 paper.

^k All attempts to chromatograph epinochrome (in 2% aqueous acetic acid) yielded, in addition to the red epinochrome spot (R_f ca. 0.80), definite spots with R_f 's of 0.44 and 0.25 due to the rearrangement product (5,6-dihydroxy-*N*-methylindole) and an unknown Ehrlich-positive substance, respectively.

^l It has recently been shown that the iodo-(or bromo-)aminochromes should be formulated as 7-iodo (or 7-bromo) derivatives and not as 2-(or 3-)halogeno derivatives [R. A. Heacock, O. Hutzinger, B. D. Scott, J. W. Daly and B. Witkop, *J. Am. Chem. Soc.* **85**, 1825 (1963)].

IV. Chemical Properties of the Aminochromes

A. STABILITY

1. In the Solid State

Some knowledge of the stability of the aminochromes in the solid state would be of considerable value to workers studying the physiological activity of these compounds, when using the same sample over a period of months or even years. However, very few systematic investigations of the solid state stability of these compounds have been made. Feldstein reported that a sample of adrenochrome prepared by his procedure and stored at 25° in a glass vial for 3 months did not undergo any noticeable changes (as determined by infrared spectroscopy; KBr disc).¹²⁵ A recent study has indicated that pure adrenochrome prepared by the method of Heacock *et al.*⁶⁴ is moderately stable for about one year under normal laboratory storage conditions.¹¹² An investigation of the purity of several of the commercial samples of adrenochrome that were available in 1962 showed them all to be of doubtful purity.¹¹² Aminochromes without a hydroxyl or alkoxy substituent in the 3-position rearrange very readily (see Section IV, B), even in the solid state. For instance, epinochrome (27) rearranges on storage *in vacuo* at 25° to 5,6-dihydroxy-*N*-methylinole (28).^{126, 127}

2. In Solution

The stability of solutions of the aminochromes is influenced by many factors such as the nature of the solvent, the pH of the medium, the nature of the buffer used (if any), the presence or absence of dissolved oxygen in the solution, the presence of traces of metal ions, traces of oxidizable organic matter, etc. In general, solutions of the aminochromes with a 3-hydroxyl group [e.g. adrenochrome (1)] are more stable than those without [e.g. epinochrome (27)].^{106, 126, 127} On the other hand, solutions of adrenochrome methyl and ethyl ethers were slightly more stable than those of adrenochrome.¹⁰⁶

The decomposition of adrenochrome solutions has usually been

¹²⁵ A. Feldstein, *Science* **128**, 28 (1958).

¹²⁶ J. Austin, J. D. Chanley, and H. Sobotka, *J. Am. Chem. Soc.* **73**, 2395 (1951).

¹²⁷ J. Austin, J. D. Chanley, and H. Sobotka, *J. Am. Chem. Soc.* **73**, 5299 (1951).

followed by observing changes in the optical density at the visible absorption maximum (see ref. 3 for a summary of early qualitative work on the stability of adrenochrome solutions). The effects of several inorganic compounds on the stability of adrenochrome solutions have recently been investigated.¹¹² (The relative rates of disappearance of adrenochrome from such solutions are shown in Table V.) Table VI shows the effect of varying the anion in a series of zinc and cupric salts on the stability of adrenochrome solutions.

TABLE V^a

EFFECT OF VARIOUS SALTS ON THE STABILITY OF AQUEOUS SOLUTIONS OF ADRENOCROME^a

Salt ^b	R ^c	Salt ^b	R ^c
HgCl ₂	0.3	Hg(OAc) ₂	3.1
MnCl ₂	0.8	NiSO ₄ ·(NH ₄) ₂ SO ₄	4.1
MgSO ₄	0.9	FeSO ₄ ·(NH ₄) ₂ SO ₄	6.8
(NH ₄) ₂ SO ₄	1.0	Zn(OAc) ₂	11.1
NaCl	1.0	Fe ₂ (SO ₄) ₃ ·(NH ₄) ₂ SO ₄	19.8
None	1.0	Cu(OAc) ₂	28.8
K ₂ SO ₄	1.1	Al ₂ (SO ₄) ₃ ·K ₂ SO ₄	40.3
CdSO ₄	1.8	Fe(NO ₃) ₃	105.0
Co(NO ₃) ₂	2.8	NH ₄ OH	256.0

^a Reproduced from the *Canadian Journal of Biochemistry and Physiology* [R. A. Heacock, G. L. Mattok, and D. L. Wilson, *Can. J. Biochem. Physiol.* **41**, 1721 (1963)] by permission of the Editor-in-Chief.

^b [Salt] = $9.4 \times 10^{-4}M$; [adrenochrome] = $2.04 \times 10^{-4}M$.

^c Relative rate of decomposition at 35°. (Absolute rates calculated by method of initial slopes.)

It can be seen from the table that the sequences are different for the two series. Adrenochrome solutions (5 $\mu g/ml$) in 0.05*N* sodium acetate were said to be stable for 4 hours; however, increasing the strength of the sodium acetate solution resulted in some decomposition of the aminochrome.¹²⁸

The rate of decomposition of adrenochrome in solution is markedly affected by the pH and temperature. Van Espen reported that adrenochrome solutions were reasonably stable at mildly acid pH's, but markedly less so in more acidic (pH 2-3) or alkaline solutions

¹²⁸ J. van Espen, *J. Pharm. Belg.* **14**, 56 (1959).

(pH 8–9).¹²⁸ Zambotti and Moret reported that the decomposition of adrenochrome solutions in aqueous buffer follows first-order kinetics, and that the rate of disappearance of the aminochrome varies linearly with pH at 37° and exponentially with temperature at pH 7.38.^{129–131} Heacock and Mattok showed that the decomposition of aqueous adrenochrome solutions follows first-order kinetics with respect to aminochrome concentration.¹⁰⁶ However, the rate of decomposition of adrenochrome solutions containing sodium hydroxide increased very rapidly with alkali concentration, and there was

TABLE VI

EFFECT OF CUPRIC AND ZINC IONS ON THE STABILITY OF AQUEOUS SOLUTIONS OF ADRENOCROME^{a, b}

Anion ^b	Relative rates ^c	
	Cu ⁺⁺	Zn ⁺⁺
SO ₄ ⁻⁻	1.8	1.4
OAc ⁻	1.4	2.5
NO ₃ ⁻	1.3	0.9
Cl ⁻	1.0	1.0

^a Reproduced from the *Canadian Journal of Biochemistry and Physiology* [R. A. Heacock, G. L. Mattok, and D. L. Wilson, *Can. J. Biochem. Physiol.* **41**, 1721 (1963)] by permission of the Editor-in-Chief.

^b [Salt] = $9.4 \times 10^{-4}M$; [adrenochrome] = $2.04 \times 10^{-4}M$.

^c Relative rates of decomposition at 35°. (Absolute rates calculated by the method of initial slopes.)

apparently no simple kinetic relationship with respect to the alkali concentration.¹⁰⁶ In 1950 Harley-Mason showed that aqueous solutions of adrenochrome decompose by a non-oxidative mechanism, the final product being an insoluble melanin.⁶ Solutions which had decomposed anaerobically in this manner contained 5,6-dihydroxy-*N*-methylindole and adrenolutin, indicating that reductive and rearrangement processes had also occurred.⁶ Decompositions of this type were shown to be markedly catalyzed by mineral acids.⁶ Bu'Lock

¹²⁹ V. Zambotti and V. Moret, *Arch. Sci. Biol. (Bologna)* **33**, 522 (1949).

¹³⁰ V. Zambotti and V. Moret, *Arch. Sci. Biol. (Bologna)* **34**, 272 (1950).

¹³¹ V. Moret, *Giorn. Biochim.* **3**, 210 (1954).

recently demonstrated that the non-oxidative decomposition of adrenochrome in acid solution was controlled by a second-order reaction between adrenochrome and the acid.¹⁰⁷

Solutions of adrenochrome in the lower aliphatic alcohols decompose rapidly; in these cases the disappearance of the adrenochrome absorption maximum in the visible region is accompanied by the appearance of the characteristic yellow-green adrenolutin fluorescence and a definite adrenolutin absorption maximum at 405 m μ appears.¹¹² The rate of rearrangement in methanol, ethanol, *n*-propanol, and *n*-butanol was about 10 times as fast as in water.¹¹² Feldstein had previously reported that adrenochrome solutions in methanol were less stable than those in water or physiological saline.¹²⁵

B. REARRANGEMENT

1. General Comments

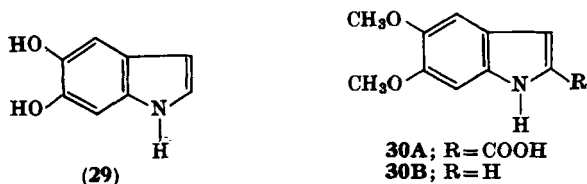
The characteristic transient yellow-green fluorescence exhibited by adrenaline solutions that were undergoing oxidation in the presence of alkali was first reported in 1918.¹³² This phenomenon was later shown to be general, and similar (but usually weaker) fluorescences were observed when other catecholamines were oxidized in alkaline solution.¹³³ Many years were to elapse before the correct explanation of this phenomenon was forthcoming, i.e. that the fluorescent product derived from adrenaline was a rearrangement product of adrenochrome (the red oxidation product of adrenaline).

In 1927 Raper showed that the red pigment obtained on oxidation of DOPA [i.e. 2,3-dihydroindole-5,6-quinone-2-carboxylic acid, dopachrome (4)] rearranged spontaneously by an "autoreduction" process *in vacuo* to 5,6-dihydroxyindole (29).⁷² The rearrangement process could be accelerated by the action of alkali or sulfur dioxide.⁷² In the latter case, decarboxylation did not accompany the rearrangement and the colorless derivative was 5,6-dihydroxyindole-2-carboxylic acid (17).⁷² Compounds 17 and 29 were isolated as their dimethyl ethers, (30A) and (30B).⁷² Immediate decolorization of epinochrome (27) solutions on addition of alkali was reported a few years later.¹³⁴

¹³² O. Lowe, *Biochem. Z.* **85**, 295 (1918).

¹³³ J. H. Gaddum and H. Schild, *J. Physiol. (London)* **80**, 9P (1933).

¹³⁴ H. Burton, *J. Chem. Soc.* 546 (1932).



Subsequent investigations have shown that Raper's suggestion that dopachrome (4) and related aminochromes decompose by an internal oxidation-reduction process forming 5,6-dihydroxyindoles was essentially correct.^{73, 118, 120, 134-137} The 5,6-dihydroxyindoles obtained from aminochromes such as dopachrome (4) and epinochrome (27) (i.e. with no substitution in the 3-position) show only a relatively weak blue to blue-mauve fluorescence.^{118, 120} The intense yellow-green fluorescence shown by the rearrangement products of aminochromes with a 3-hydroxyl group is due to the formation of 5,6-dihydroxyindoxyls by the rearrangement process. However, despite the striking differences in the fluorescence properties of the products, all aminochromes (with the possible exception of those with a 3-alkoxy substituent) undergo essentially the same type of internal oxidation-reduction reaction.

2. Rearrangements in Water and Aqueous Alkali

All aminochromes undergo a slow spontaneous rearrangement in aqueous solution, although the rate is considerably affected by the structure of the aminochrome in question. The rearrangement of all aminochromes is however markedly catalyzed by alkali (see ref. 3 for early references). The structure of the fluorescent alkaline rearrangement product of adrenochrome was not ascertained until 30 years after the characteristic fluorescence reaction had been first reported,¹³⁸ and the substance [i.e. adrenolutin, 5,6-dihydroxy-*N*-methylindoxyl (31), often formulated as 3,5,6-trihydroxy-*N*-methylindole (32), cf. refs. 3, 108] was finally isolated in crystalline form in 1949.^{139, 140} Subsequently, *N*-ethyl-5,6-dihydroxyindoxyl (33) and 5,6-dihydroxy-*N*-isopropylindoxyl (34) have been isolated in crystal-

¹³⁵ H. S. Mason, *J. Biol. Chem.* **168**, 433 (1947).

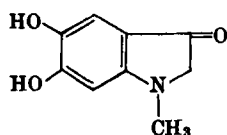
¹³⁶ H. S. Mason, *J. Biol. Chem.* **172**, 83 (1948).

¹³⁷ H. S. Mason and C. I. Wright, *J. Biol. Chem.* **180**, 235 (1949).

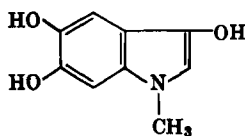
¹³⁸ I. Ehrlén, *Farm. Revy* **47**, 242 (1948); *Chem. Abstr.* **42**, 5166 (1948).

¹³⁹ A. Lund, *Acta Pharmacol. Toxicol.* **5**, 75 (1949).

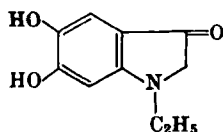
¹⁴⁰ A. Lund, *Acta Pharmacol. Toxicol.* **5**, 121 (1949).



(31)



(32)



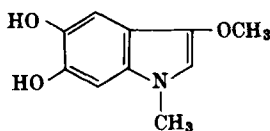
(33)



(34)

line form from the alkaline rearrangement products of *N*-ethyl- and *N*-isopropyl-noradrenochrome, respectively.^{65, 74} Both of these substances exhibit an intense yellow-green fluorescence similar to that of adrenolutin in ultraviolet light.^{65, 74}

The red color of adrenochrome methyl ether (8) solutions is rapidly discharged on addition of alkali, with the formation of a dirty brown, essentially non-fluorescent, solution from which an unidentified dark grey amorphous product was obtained on acidification,¹¹⁰ possibly 5,6-dihydroxy-3-methoxy-*N*-methylindole (35) and not 5,6-dihy-



(35)

droxy-3-methoxyindole as was erroneously reported in the literature.¹¹⁰

The rearrangements of adrenochrome (1) and adrenochrome methyl ether (8) in water and alkali are first order with respect to aminochrome concentration.¹⁰⁶ However, no simple kinetic relationship between the rate of rearrangement and alkali concentration was found; the rate of rearrangement in the presence of sodium hydroxide increased very rapidly with increasing alkali concentration.¹⁰⁶

3. Rearrangements Catalyzed by Metal Ions

The rearrangement of the aminochromes to 5,6-dihydroxyindoles or 5,6-dihydroxyindoxyls is catalyzed by zinc salts (and less readily

by aluminum salts). This phenomenon was first described by Fischer *et al.*^{141, 142} and subsequently used for the preparation of a number of 5,6-dihydroxyindoles by Bu'Lock and Harley-Mason.^{104, 143} Although zinc and aluminum ions were considered to be unique among metal ions in catalyzing this rearrangement,¹⁴² it has recently been shown by Heacock *et al.* that an adrenolutin-like fluorescence can also be detected in solutions of adrenochrome that have been allowed to decompose in the presence of cadmium and nickel ions.¹¹² The possibility that other ions catalyze this rearrangement cannot be totally excluded on the basis of fluorimetric measurements, since many metal ions are known to quench the fluorescence of adrenolutin (e.g. Cu^{++} ¹⁴⁴); consequently, the fluorescence of any adrenolutin that had been formed would not be observed.

The zinc acetate-catalyzed rearrangement of adrenochrome and its methyl ether has recently been shown by Heacock and Mattok to be first order with respect to both aminochrome and zinc acetate concentrations.¹⁰⁶ The zinc acetate-catalyzed rearrangement products of aminochromes with no 3-substituent or with a 3-hydroxyl group are basically the same as those obtained with alkali. However, in the case of the 3-alkoxyaminochromes the major product obtained on treatment with zinc acetate is a dark blue zinc-containing insoluble compound of uncertain composition.^{106, 110} (Microanalysis suggested a hydrated 1:2 zinc-aminochrome complex.)¹⁰⁶

4. Rearrangements in Non-Aqueous Media

a. *In Aliphatic Alcohols.* Adrenochrome rearranges to adrenolutin quite rapidly in the lower aliphatic alcohols; the rate of rearrangement is about ten times as fast as in water.¹¹²

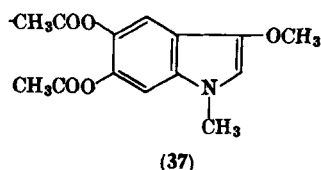
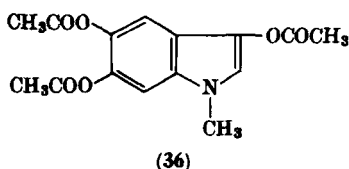
b. *Rearrangements with Acetic Anhydride and Pyridine.* Treatment of adrenochrome (1) with acetic anhydride in pyridine gave 3,5,6-triacetoxy-*N*-methylindole (36),⁶ rearrangement being accompanied by acetylation. This reaction was subsequently shown to be general,^{65, 70, 71, 74, 104, 109, 126, 127} and a number of 3,5,6-triacetoxy- and 5,6-diacetoxy-indoles have been prepared from aminochromes with and without the 3-hydroxyl group, respectively. The 3-alkoxy-

¹⁴¹ P. Fischer and G. Derouaux, *Compt. Rend. Soc. Biol.* **144**, 707 (1950).

¹⁴² P. Fischer, G. Derouaux, H. Lambot, and J. Lecomte, *Bull. Soc. Chim. Belges* **59**, 72 (1950).

¹⁴³ J. Harley-Mason and J. D. Bu'Lock, *Nature* **166**, 1036 (1950).

¹⁴⁴ J. G. L. Harthorn, *J. Pharm. Pharmacol.* **11**, 553 (1959).



aminochromes appear to behave normally with acetic anhydride and pyridine; e.g., adrenochrome methyl ether (8) gave 5,6-diacetoxy-3-methoxy-*N*-methylindole (37) on treatment with these reagents.⁶⁵ A number of di- and tri-acetoxy derivatives of this type which have been prepared in this manner are listed in Table VII.

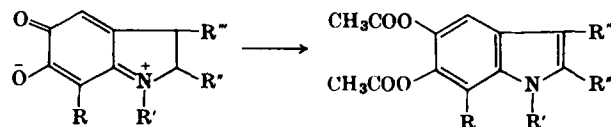
It has not yet been possible to isolate noradrenolutin from the products of the direct rearrangement of noradrenochrome in solution. [Noradrenolutin should probably be formulated in the keto form (38); however, it is often represented in the trihydroxy form (39).] However, pure samples of this valuable compound have recently been obtained by the cautious hydrolysis of 3,5,6-triacetoxyindole (40),^{70, 71} obtained by deiodination of 3,5,6-triacetoxy-7-iodoindole (41),^{70, 71} which can readily be obtained by the action of acetic anhydride and pyridine on 7-iodonoradrenochrome (42).^{70, 71, 74} 7-Iodonoradrenochrome (42) has been prepared in pure crystalline form by the oxidation of noradrenaline (43) with potassium iodate.^{70, 71}

In view of the fact that halogen substitution occurs at the 7-position in the aminochrome nucleus and not the 2-position as previously supposed (see Section IV, E), it would now appear that the action of acetic anhydride and pyridine on the aminochrome obtained from the reaction of potassium iodate with α -methylnoradrenaline (44) [i.e. 7-iodo-2-methylnoradrenochrome (45)⁷⁰ and not 2-iodo-2-methylnoradrenochrome (46)⁷⁴] follows the normal course. The initial product is 3,5,6-triacetoxy-7-iodo-2-methylindole (47)⁷⁰ [which gives 3,5,6-triacetoxy-2-methylindole (48) on deiodination⁷⁰] and not 5,6-diacetoxy-*N*-acetyl-2-iodo-2-methylindoxyl (49) as suggested by Bu'Lock and Harley-Mason.⁷⁴ Compound 49 was said to give 5,6-diacetoxy-*N*-acetyl-3-hydroxy-2-methylindole (50) on deiodination.⁷⁴

5. Mechanism of the Rearrangement

The overall reaction consists of the removal of protons from the 2- and 3-positions of the five-membered ring of the aminochrome system and the addition of a proton to each of the C-5 and C-6

TABLE VII
ACETIC ANHYDRIDE-PYRIDINE REARRANGEMENT PRODUCTS



Aminochrome rearranged	R	R'	R''	R'''	Product	R	R'	R''	R'''	Melting point, °C
Adrenochrome	H	CH ₃	H	OH	3,5,6-triacetoxy- <i>N</i> -methylindole ^a	H	CH ₃	H	OCOCH ₃	112-113
<i>N</i> -Ethylnoradrenochrome	H	C ₂ H ₅	H	OH	3,5,6-triacetoxy- <i>N</i> -ethylindole ^b	H	C ₂ H ₅	H	OCOCH ₃	84.5-85.5
<i>N</i> -Isopropylnoradrenochrome	H	<i>i</i> -C ₃ H ₇	H	OH	3,5,6-triacetoxy- <i>N</i> -isopropylindole ^b	H	<i>i</i> -C ₃ H ₇	H	OCOCH ₃	85.5-87.5
Adrenochrome methyl ether	H	CH ₃	H	OCH ₃	5,6-diacetoxy-3-methoxy- <i>N</i> -methylindole ^b	H	CH ₃	H	OCH ₃	140-141
Adrenochrome ethyl ether	H	CH ₃	H	OC ₂ H ₅	5,6-diacetoxy-3-ethoxy- <i>N</i> -methylindole ^b	H	CH ₃	H	OC ₂ H ₅	84.5-85.5
2-Methylnoradrenochrome	H	H	CH ₃	OH	3,5,6-triacetoxy-2-methylindole ^c	H	H	CH ₃	OCOCH ₃	187-188 ^d
Epinochrome	H	CH ₃	H	H	5,6-diacetoxy- <i>N</i> -methylindole ^e	H	CH ₃	H	H	101-102 ^f
7-Iodonoradrenochrome ^g	I	H	H	OH	3,5,6-triacetoxy-7-iodoindole ^{c, g}	I	H	H	OCOCH ₃	207-208
7-Ioadrenochrome ^g	I	CH ₃	H	OH	3,5,6-triacetoxy-7-iodo- <i>N</i> -methylindole ^{g-h}	I	CH ₃	H	OCOCH ₃	150.5

<i>N</i> -Ethyl-7-iodonoradrenochrome ^g	I	C ₂ H ₅	H	OH	3,5,6-triacetoxy- <i>N</i> -ethyl-7-iodoindole ^{b, g}	I	C ₂ H ₅	H	OCOCH ₃	142–143.5
7-Iodo- <i>N</i> -isopropylnoradrenochrome ^g	I	<i>i</i> -C ₃ H ₇	H	OH	3,5,6-triacetoxy-7-iodo- <i>N</i> -isopropylindole ^{g, h}	I	<i>i</i> -C ₃ H ₇	H	OCOCH ₃	163–164
7-Iodoadrenochrome methyl ether ^g	I	CH ₃	H	OCH ₃	5,6-diacetoxy-3-methoxy-7-iodo- <i>N</i> -methylindole ^{b, g}	I	CH ₃	H	OCH ₃	191–192
7-Iodoadrenochrome ethyl ether ^g	I	CH ₃	H	OC ₂ H ₅	5,6-diacetoxy-3-ethoxy-7-iodo- <i>N</i> -methylindole ^{b, g}	I	CH ₃	H	OC ₂ H ₅	149.5
7-Iodo-2-methylnoradrenochrome ^g	I	H	CH ₃	OH	3,5,6-triacetoxy-7-iodo-2-methylindole ^{c, g, h}	I	H	CH ₃	OCOCH ₃	205
7-Iodonorepinochrome ^g	I	H	H	H	5,6-diacetoxy-7-iodoindole ^{g, j}	I	H	H	H	126
7-Iodoepinochrome ^g	I	CH ₃	H	H	5,6-diacetoxy-7-iodo- <i>N</i> -methylindole ^{g, i, k}	I	CH ₃	H	H	148–150
7-Bromoadrenochrome ^g	Br	CH ₃	H	OH	3,5,6-triacetoxy-7-bromo- <i>N</i> -methylindole ^{c, g}	Br	CH ₃	H	OCOCH ₃	137.5–138.5

^a J. Harley-Mason, *J. Chem. Soc.* 1276 (1950).

^b R. A. Heacock and B. D. Scott, *Can. J. Chem.* **38**, 516 (1960).

^c R. A. Heacock, O. Hutzinger, B. D. Scott, J. W. Daly, and B. Witkop, *J. Am. Chem. Soc.* **85**, 1825 (1963).

^d Samples of this compound of higher purity (m.p. 194–195°) are more conveniently prepared by deiodination of 3,5,6-triacetoxy-7-iodo-2-methylindole [R. A. Heacock *et al.*, *loc. cit.* (footnote "c")].

^e J. Austin, J. D. Chanley, and H. Sobotka, *J. Am. Chem. Soc.* **73**, 5299 (1951).

^f Somewhat higher melting points have been reported for 5,6-diacetoxy-*N*-methylindole (prepared by acetylation of 5,6-dihydroxy-*N*-methylindole); i.e., 104–105° [J. Harley-Mason, *J. Chem. Soc.* 1276 (1950)] and 109–110° [R. A. Heacock, M. E. Mahon, and B. D. Scott, *Can. J. Chem.* **39**, 231 (1961)].

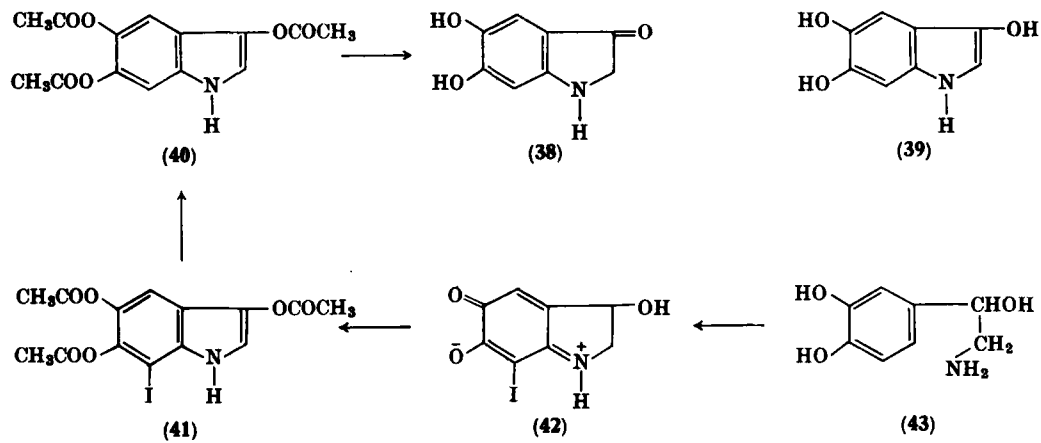
^g It has recently been shown that the iodo-(or bromo-)aminochromes should be formulated as 7-iodo (or 7-bromo) derivatives and not as 2-(or 3-)halogeno derivatives [R. A. Heacock *et al.*, *loc. cit.* (footnote "c")].

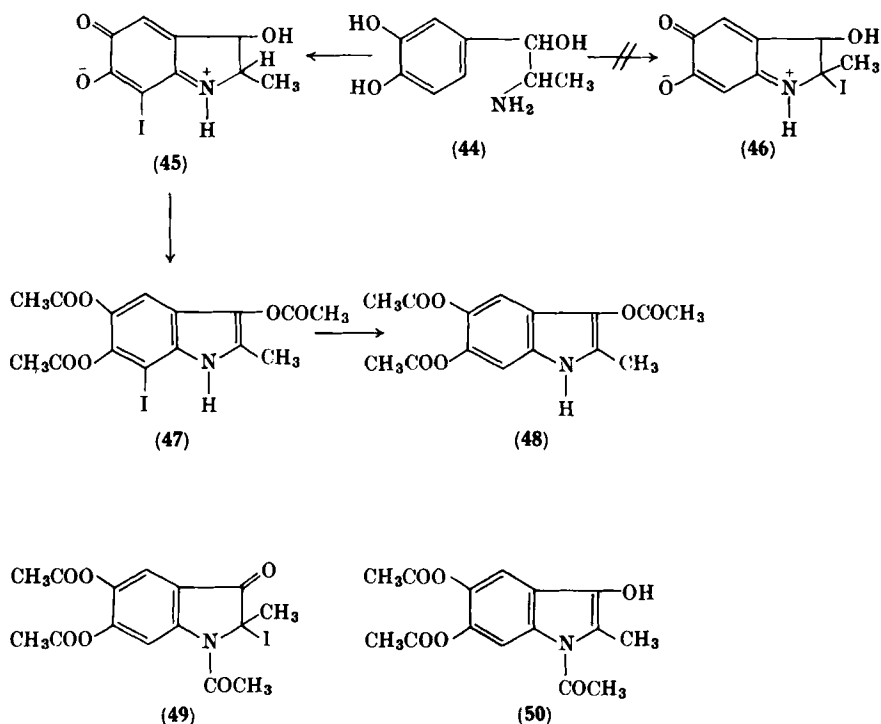
^h J. D. Bu'Lock and J. Harley-Mason, *J. Chem. Soc.* 712 (1951).

ⁱ R. A. Heacock and B. D. Scott, *Can. J. Chem.* **38**, 508 (1960).

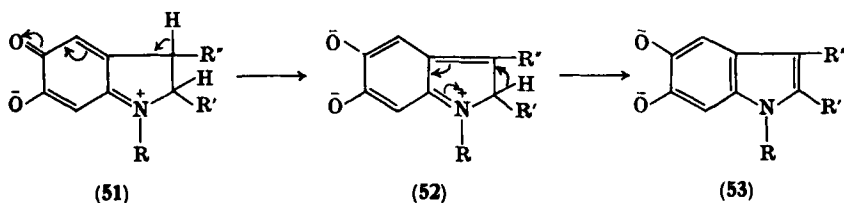
^j R. A. Heacock and B. D. Scott, unpublished work (1962).

^k J. D. Bu'Lock and J. Harley-Mason, *J. Chem. Soc.* 2248 (1951).





carbonyl oxygen atoms of the *o*-quinonoid ring. Heacock and Mattok have demonstrated that the rearrangements of adrenochrome and adrenochrome methyl ether show good first-order dependency on aminochrome concentration in aqueous alkali and aqueous zinc acetate.¹⁰⁶ Further work with a series of aminochromes showed that the rates of rearrangement were strongly affected by substituents at C-3 (see Table VIII) whilst those at the 2-position had little effect.¹⁰⁶ The entropy term in the case of epinochrome (27) (no C-3 substituents) was shown to be slightly more favorable for rearrangement than in the other cases.¹⁰⁶ This would have been expected if the rate-determining process was the removal of a proton from C-3. Heacock and Mattok concluded that the rate-determining process was the removal of a proton from C-3 and that this step was followed by the series of electron shifts as shown in the reaction scheme $51 \rightarrow 52 \rightarrow 53$.¹⁰⁶ A similar mechanism had been proposed earlier by Sobotka *et al.*, but without supporting physico-chemical data.² The rate of rearrangement would, therefore, be expected to decrease with an



increase in the electron-attracting capacity of the C-3 substituent, and this was in fact observed¹⁰⁶ (see Table VIII). The *N*-substituents also affected the rates of rearrangement in the manner that would have been expected from the inductive effects of these groups (see Table VIII).

The rapid increase in the rate of rearrangement with increasing alkali concentration indicated that the OH⁻ ions probably assist

TABLE VIII

REARRANGEMENT OF SEVERAL AMINOCHROMES IN VARIOUS REACTION MEDIA^a

Aminochrome ^b	R	R'	R''	$k_1 \times 10^4 \text{ (min}^{-1}\text{)}^c$		
				H ₂ O	NaOH ^b	Zn(OAc) ₂ ^b
Epinochrome	CH ₃	H	H	14.6	72.1	126.0
Adrenochrome	CH ₃	H	OH	2.04	22.4	13.4
Adrenochrome methyl ether	CH ₃	H	OCH ₃	1.26	15.3	10.4
Adrenochrome ethyl ether	CH ₃	H	OC ₂ H ₅	0.76	10.2	9.77
<i>N</i> -Isopropylnoradrenochrome	<i>i</i> -C ₃ H ₇	H	OH	3.72	41.7	19.5
Noradrenochrome ^d	H	H	OH	1.48	12.3	11.9
2-Methyladrenochrome	CH ₃	CH ₃	OH	1.80	17.3	16.3
<i>N</i> -Ethyl-2-methylnoradrenochrome	C ₂ H ₅	CH ₃	OH	1.80	19.3	18.8

^a Reproduced from the *Canadian Journal of Chemistry* [R. A. Heacock and G. L. Mattok, *Can. J. Chem.* **41**, 139 (1963)] by permission of the Editor-in-Chief.

^b Initial concentrations of reagents: NaOH = $8.50 \times 10^{-5} M$; Zn(OAc)₂ = $9.50 \times 10^{-4} M$; and aminochrome = $2.05 \times 10^{-4} M$.

^c Rate constants at 35°.

^d The rates obtained for noradrenochrome were not as reliable as those for the other aminochromes due to the difficulties experienced in obtaining pure solutions of noradrenochrome [cf. R. A. Heacock and G. L. Mattok, *loc. cit.* (footnote "a")].

several processes simultaneously, thus accounting for the lack of a simple kinetic relationship with respect to alkali concentration. Several of the observed kinetic and thermodynamic features of the zinc acetate-catalyzed rearrangements were similar to those observed for the alkali catalyzed and uncatalyzed rearrangements (i.e. similar substituent effects). However, good first-order dependancy on the zinc acetate concentration was observed.¹⁰⁶ Kinetic data suggested that the initial reaction occurred between one aminochrome molecule and one zinc acetate molecule,¹⁰⁶ instead of the 2:1 (aminochrome-zinc) interaction previously proposed by Bu'Lock and Harley-Mason.¹⁰⁴ Presumably the Zn^{++} ion induces electromeric shifts in the aminochrome molecule similar to those that occur in the alkali-catalyzed rearrangements. The blue insoluble precipitate obtained from adrenochrome methyl ether with zinc acetate may be a hydrated 2:1 (aminochrome-zinc) complex.¹⁰⁶ A complex of this nature could be formed by interaction of an initial 1:1 complex (as required by the kinetic data) with another aminochrome molecule.¹⁰⁶

The mechanisms of the rearrangements of the aminochromes in the presence of alkali or zinc acetate differ mainly in the method by which the two catalysts bring about essentially the same electronic changes in the aminochrome molecule.¹⁰⁶

C. REDUCTION

1. Introduction

The aminochromes possess an *o*-quinone function and are therefore easily reduced; the intense color of their solutions is readily discharged by the action of most common reducing agents. The fact that adrenochrome and its 7-iodo derivative are easily reduced was reported at the same time as the isolation of these products was described.^{69, 145, 146} Early workers, not unreasonably, suggested that reduction of an aminochrome simply resulted in the formation of the corresponding "leucoaminochrome," i.e. a 5,6-dihydroxyindoline derivative. However, subsequent investigations suggested that the picture was in fact much more complicated. In general, the reaction was not reversible (as might have been expected), and different reducing agents appeared to produce different "leuco" compounds (see refs. 2 and 3 for a summary of early references on aminochrome reduction).

¹⁴⁵ D. E. Green and D. Richter, *Biochem. J.* **31**, 596 (1937).

¹⁴⁶ F. Bergel and A. L. Morrison, *J. Chem. Soc.* **48** (1943).

Progress in understanding the nature of the reactions that take place on treatment of aminochromes with reducing agents has been hampered by a number of factors, including (i) the possibility of the aminochrome rearranging (see Section IV, B) under the influence of the reducing agent, particularly in the case of aminochromes with no hydroxyl or alkoxyl group in the 3-position; (ii) difficulties in differentiating between primary and secondary products (the latter could be formed by interaction of the initially formed reduction products with excess reducing agent or oxidized reducing agent, or by the reaction of unchanged aminochrome with the oxidized reducing agent); (iii) the instability of many of the products, making their isolation in realistic yields difficult; and (iv) the fact that sodium bisulfite does not reduce the aminochromes but merely forms stable addition products with them (see Section IV, F).

Recently the reaction mixtures obtained by treating the aminochromes with several different reducing agents have been examined paper chromatographically. This procedure has afforded considerable information about the total reaction mixtures, particularly since many of the products are water-soluble and not readily extracted by organic solvents. The most satisfactory chromatographic systems for studying aminochrome reduction mixtures, and similar reaction mixtures, i.e. those obtained during the decomposition of certain aminochrome solutions, were found to be water or 2% aqueous acetic acid used in conjunction with acid-washed Whatman No. 1 paper.^{89, 109, 118-123, 147-150}

2. Reductions with Sodium Hydrosulfite

Sodium hydrosulfite (i.e. sodium dithionite, $\text{Na}_2\text{S}_2\text{O}_4$) has been used extensively for reduction of the aminochromes.^{5, 6, 65, 70, 74, 102, 104, 109, 118-120, 123, 148, 151-155} Heacock and Scott showed by paper chromatography that two major products were obtained from

¹⁴⁷ R. A. Heacock and B. D. Laidlaw, *Nature* **182**, 526 (1958).

¹⁴⁸ R. A. Heacock and B. D. Laidlaw, *Chem. Ind. (London)* 1510 (1958).

¹⁴⁹ R. A. Heacock and B. D. Scott, *Can. J. Biochem. Physiol.* **37**, 1087 (1959).

¹⁵⁰ G. L. Mattok and R. A. Heacock, *Nature* **198**, 993 (1963).

¹⁵¹ R. A. Heacock, M. E. Mahon, and B. D. Scott, *Can. J. Chem.* **39**, 231 (1961).

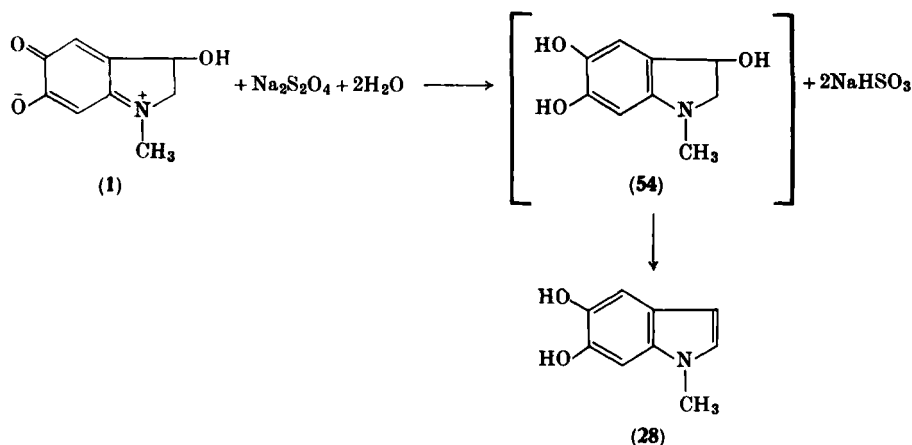
¹⁵² P. Fischer, *Bull. Soc. Chim. Belges* **58**, 205 (1949).

¹⁵³ P. Fischer and J. Lecomte, *Bull. Soc. Chim. Biol.* **33**, 569 (1951).

¹⁵⁴ S. Tanaka and S. Miyata, *Wakayama Med. Rept.* **2**, 51 (1954); *Chem. Abstr.* **49**, 9054 (1955).

¹⁵⁵ R. A. Heacock and B. D. Scott, unpublished work (1960-1964).

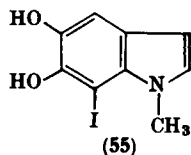
adrenochrome (1) on treatment with sodium hydrosulfite, namely 5,6-dihydroxy-*N*-methylindole (28) and the adrenochrome-sodium bisulfite addition product^{148, 155} (see Section IV, F). Compound 28 is produced by the spontaneous irreversible dehydration of the initially formed "leuco-adrenochrome," i.e. 3,5,6-trihydroxy-*N*-methylindoline (54). The latter compound was presumably formed by the interaction of some of the unchanged adrenochrome with sodium bisulfite (formed by oxidation of some of the reducing agent). 5,6-Dihydroxyindoles also form complexes readily with sodium bisulfite,^{118, 123, 156} and the presence of the 5,6-dihydroxy-*N*-methylindole-sodium bisulfite addition complex among the products obtained



from the reaction of adrenochrome with $\text{Na}_2\text{S}_2\text{O}_4$, along with other as yet unidentified products, has recently been observed.¹⁵⁵ *N*-Ethyl-noradrenochrome and *N*-isopropyl-noradrenochrome behave analogously on reduction with $\text{Na}_2\text{S}_2\text{O}_4$.^{151, 155} Adrenochrome methyl and ethyl ethers gave products similar to those obtained from adrenochrome on reduction with $\text{Na}_2\text{S}_2\text{O}_4$ indicating that the intermediate "leuco-aminochrome ethers" (i.e. a 3-alkoxy-5,6-dihydroxy-*N*-methylindoline) lose methanol from the 2- and 3-positions of the five-membered ring as readily as "leuco-adrenochrome" (54) loses the elements of water from the 2- and 3-positions of the 3,5,6-trihydroxyindoline ring system.¹⁵⁵ Reduction of the 7-iodoaminochromes with $\text{Na}_2\text{S}_2\text{O}_4$ gave a complex mixture of products.^{109, 155}

¹⁵⁶ R. A. Heacock and B. D. Scott, *Biochim. Biophys. Acta* **62**, 591 (1962).

One of the main products in each case was the expected 5,6-dihydroxy-7-iodoindole,^{70, 109, 119, 151, 155} which was invariably accompanied by some of the corresponding deiodinated product.¹⁵⁵ (The elimination of the halogen atom in reactions of this type has been referred to previously.¹⁰⁹) Reduction of 7-iodoadrenochrome (12) with $\text{Na}_2\text{S}_2\text{O}_4$ gives, besides 5,6-dihydroxy-7-iodo-*N*-methylindole (55) and 5,6-dihydroxy-*N*-methylindole (28), the sodium bisulfite



addition products of 7-iodoadrenochrome (12), adrenochrome (1), 5,6-dihydroxy-7-iodo-*N*-methylindole (55), and 5,6-dihydroxy-*N*-methylindole (28) together with a number of unidentified minor products.¹⁵⁵ Although these addition complexes could not be separated paper chromatographically, Bouchilloux has reported that it is possible to differentiate between the sodium bisulfite addition products of 1 and 12 by paper electrophoresis.¹¹⁹

The other iodoaminochromes (and bromoadrenochrome) behave similarly on treatment with $\text{Na}_2\text{S}_2\text{O}_4$, although there appears to be less tendency for the bromine atom to be eliminated during the reduction process.^{6, 155}

3. Reductions with Sodium Borohydride

The alkali metal borohydrides reduce aminochromes in solution very rapidly^{70, 109, 120, 147, 148, 151, 155, 157}; the expected 5,6-dihydroxyindole derivative was usually obtained in high yield.^{151, 155} Reduction of the 7-iodoaminochromes was not usually accompanied by deiodination to any appreciable extent.^{109, 155} A number of relatively minor, unidentified, often fluorescent, water-soluble by-products were usually also detected in the reduction mixtures.^{109, 148, 155}

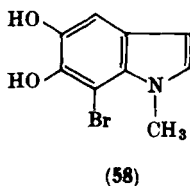
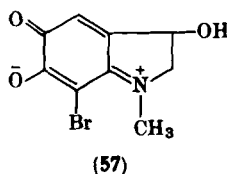
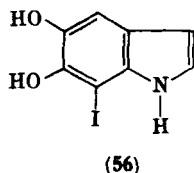
4. Reductions with Zinc and Dilute Acetic Acid

Zinc and dilute acetic acid reduce aminochromes in solution very rapidly giving the expected 5,6-dihydroxyindole in high yield.^{148, 151, 155} The reduction reaction apparently takes precedence

¹⁵⁷ P. Mesnard and J. Marzat, *Bull. Soc. Chim. France* 895 (1954).

in this case over the rearrangement process, which is known to be catalyzed by Zn^{++} ions (see Section IV, B, 3) (cf. refs. 104, 106, 141–143).

Reduction of the 7-iodoaminochromes⁷⁰ with zinc and dilute acid was usually accompanied by virtually complete elimination of the iodine atom,^{109, 155} except in the case of 7-iodonoradrenochrome (42), where, although the main product was 5,6-dihydroxyindole (29), traces of 5,6-dihydroxy-7-iodoindole (56) were also detected.¹⁵⁵ Only partial debromination was observed when 7-bromoadrenochrome (57) was reduced with this system; 7-bromo-5,6-dihydroxy-*N*-methylindole (58) and 5,6-dihydroxy-*N*-methylindole (28) were both obtained in significant quantities.¹⁵⁵

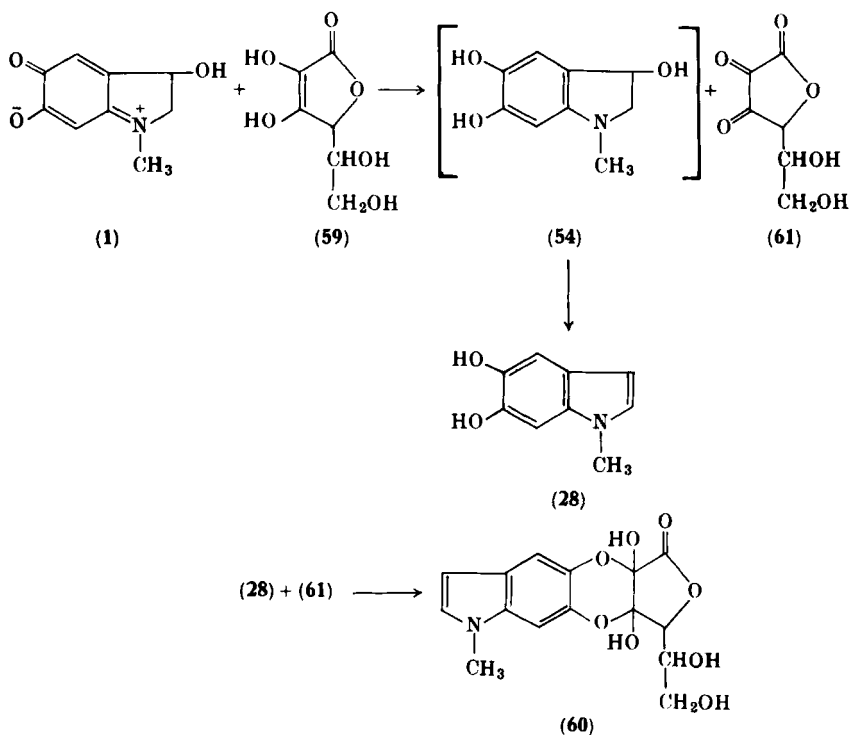


5. Reductions with Ascorbic Acid

The reduction of adrenochrome (1) with ascorbic acid (59) was first reported in 1948,¹⁵⁸ although the nature of the reaction products (which may be of physiological importance, cf. ref. 159) was not determined until several years later. It was shown by Heacock and Laidlaw in 1958 that reduction mixtures of this type contained at least three indolic products,¹⁴⁷ one of which was isolated and shown to be 5,6-dihydroxy-*N*-methylindole (28).¹⁴⁷ The major component of aqueous adrenochrome-ascorbic acid reaction mixtures has recently been shown to be a secondary product (60) (which was isolated as its di- and tetra-acetyl derivatives) produced by the interaction of the *o*-dihydroxy group of 28 with the α -dicarbonyl function of dehydro-

¹⁵⁸ A. Beauvillain and J. Sarradin, *Bull. Soc. Chim. Biol.* **30**, 478 (1948).

¹⁵⁹ S. Roston, *Nature* **194**, 1079 (1962).

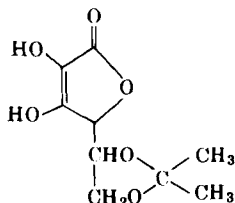


ascorbic acid (**61**) (produced by oxidation of some of the ascorbic acid present in the system).^{150, 160} Reduction of adrenochrome by ascorbic acid in a water-ether system did not give rise to **60**, since under these conditions any **28** initially produced was preferentially extracted into the ether layer, thus preventing its interaction with any **61** produced in the aqueous phase.^{150, 160, 161} This procedure has been adapted as a convenient preparative method for 5,6-dihydroxy-*N*-methylindole (**28**).¹⁶¹ The simple homologues of adrenochrome behave in an analogous manner on reduction by ascorbic acid,¹⁵⁵ as do the halogenated aminochromes, although in the latter case the mixtures of products are more complex, due to the presence of small but significant amounts of the corresponding deiodinated products along with the 5,6-dihydroxy-7-iodoindoles and the "7-iodo" homologues of **60**.¹⁵⁵

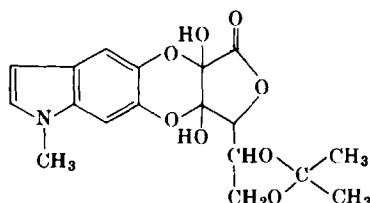
¹⁶⁰ G. L. Mattok and R. A. Heacock, *Can. J. Chem.* **42**, 1401 (1964).

¹⁶¹ G. L. Mattok and R. A. Heacock, *Can. J. Chem.* **42**, 484 (1964).

5,6-Isopropylideneascorbic acid (62) has recently been shown to reduce adrenochrome in a similar manner to ascorbic acid; the main products are 28 and an isopropylidene derivative of 60, i.e. 63.¹⁶⁰



(62)



(63)

6. Reductions with Thiols

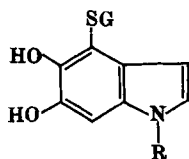
a. *Hydrogen sulfide*. The reduction of adrenochrome by hydrogen sulfide was first reported in 1937.¹⁴⁵ It has subsequently been shown that the main product is 5,6-dihydroxy-*N*-methylindole (i.e. the dehydrated "leuco-compound") and that it is formed in high yield.^{149, 155} The simple homologues of adrenochrome behave analogously.¹⁵⁵ The halogenated aminochromes are reduced to the corresponding halogenated 5,6-dihydroxyindoles in good yield with hydrogen sulfide, and there is very little evidence of deiodination occurring during the reduction process.¹⁵⁵

b. *B.A.L. (2,3-Dimercapto-1-propanol)*. The aminochromes are reduced very rapidly with B.A.L.^{12, 149, 155} Adrenochrome (1) reacts with this reagent to give mainly 5,6-dihydroxy-*N*-methylindole (28) and a second unidentified substance showing an intense yellow fluorescence in ultraviolet light and giving indole color reactions, together with other unidentified minor by-products.^{149, 155} The simple homologues of adrenochrome behave similarly on reduction with B.A.L.¹⁵⁵

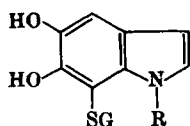
Reduction of the 7-iodo- and 7-bromo-aminochromes with this reagent gives more complex mixtures of products. The reduction process is accompanied by a considerable amount of dehalogenation in each case, and both the expected halogeno-5,6-dihydroxyindole and the corresponding 5,6-dihydroxyindoles are produced.¹⁵⁵ Traces of products, similar to the unidentified fluorescent product obtained from adrenochrome, were usually also detected chromatographically, together with several minor unidentified products.¹⁵⁵

c. *Glutathione*. It has been shown by paper chromatography that

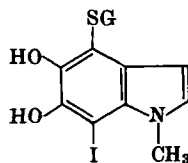
although 5,6-dihydroxy-*N*-methylindole (28) is produced when adrenochrome (1) is reduced by glutathione¹⁶² in aqueous solution other products (not ether-extractable) are formed at the same time.^{148, 149, 155} The main ether-insoluble product exhibits color reactions typical of (i) an indole, (ii) a catechol, and (iii) an α -amino acid.^{148, 155} This product (which has an R_f value of *ca.* 0.60 in 2% acetic acid) may be similar to a substance obtained by Bouchilloux and Kodja either by the reduction of dopachrome (4) with glutathione or by the oxidation of 5,6-dihydroxyindole (29) in the presence of glutathione,^{89, 122} and described as *S*-[4-(5,6-dihydroxyindolyl)]-glutathione (64A) [or possibly the corresponding 7-indolyl compound (65A)]. The main product, which was not extractable with ether, obtained from the reaction of adrenochrome with glutathione could,



64A; R = H
64B; R = CH₃



65A; R = H
65B; R = CH₃



(66)

(GSH = glutathione)

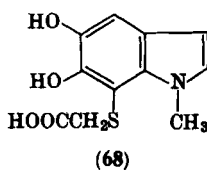
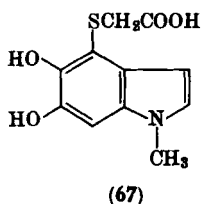
therefore, possibly be *S*-[4-(5,6-dihydroxy-*N*-methylindolyl)]glutathione (64B) [or the corresponding 7-isomer (65B)]. Unchanged glutathione, oxidized glutathione, and a third non-ether-extractable indolic product (unidentified) were also present in the reaction mixtures.¹⁵⁵ *N*-Ethyl- and *N*-isopropyl-noradrenochrome appear to give mixtures of products analogous to those obtained from 1 on reduction with glutathione.¹⁵⁵ (See *Notes Added in Proof*, p. 287.)

Reduction of 7-iodoadrenochrome (12) with glutathione gave a complex mixture of products.¹⁵⁵ The main product appeared to be chromatographically similar to the glutathione-5,6-dihydroxy-*N*-methylindole complex obtained from adrenochrome (cf. 64B or 65B). However, both the expected 5,6-dihydroxy-7-iodo-*N*-methylindole (55) and the corresponding deiodinated product (28) were also detected in the reaction mixture,¹⁵⁵ together with a compound which is possibly

¹⁶² Glutathione, a biologically important tripeptide, has the following structure in the reduced form: HOOCCH(NH₂)CH₂CH₂CONHCH(CH₂SH)-CONHCH₂COOH.

a 5,6-dihydroxy-7-iodo-*N*-methylindole-glutathione complex (66).¹⁵⁵ 7-Bromoadrenochrome (57) and 7-iodonoradrenochrome (42) behave somewhat differently on reduction with glutathione; the main product obtained in both these cases was probably the halogenated complex (cf. 66), together with 7-bromo-5,6-dihydroxy-*N*-methylindole (58) and 5,6-dihydroxy-7-iodoindole (56), respectively, and smaller quantities of the corresponding dehalogenated products.¹⁵⁵

d. *Thioglycollic Acid*. The aminochromes are reduced very rapidly by thioglycollic acid.^{149, 155} The main products obtained from adrenochrome (1) are 5,6-dihydroxy-*N*-methylindole (28) and a substance which is possibly *S*-[4-(5,6-dihydroxy-*N*-methylindolyl)]-thioglycollic acid (67) or the corresponding 7-indolyl compound (68).¹⁵⁵ A third minor, but consistently present, product was also



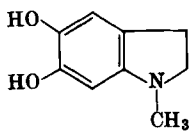
detected by paper chromatography among the reaction products.^{149, 155} The other non-halogenated aminochromes gave analogous products on reduction with thioglycollic acid.¹⁵⁵ Reduction of the 7-iodoaminochromes with thioglycollic acid gave both the expected *N*-alkyl-5,6-dihydroxy-7-iodoindoles and the corresponding deiodinated products, together with their thioglycollic acid conjugates.¹⁵⁵

e. *Miscellaneous Organic Sulfur Compounds*. Several other organic compounds containing sulfur have also been reported to reduce the aminochromes, although they have been less extensively studied than the compounds mentioned above. They include cysteine,^{89, 122, 148, 149} penicillamine (β,β -dimethylcysteine),¹⁴⁹ and thiourea dioxide.¹⁴⁸ It was shown paper chromatographically that complex mixtures of products were obtained from adrenochrome (1) with these three reagents, but 5,6-dihydroxy-*N*-methylindole (28) was invariably one of the products.¹⁴⁹ Ergothioneine appeared to react anomalously with 1 since no 28 was detected among the reaction products¹⁴⁹; however, this is not altogether surprising since

the thiol group in ergothioneine is quite different in character from the other thiols studied (cf. Bell¹⁶³).

7. Mechanism of Aminochrome Reduction

Aminochromes which have no hydroxy or alkoxy substituent in the 3-position rearrange to the corresponding 5,6-dihydroxyindole extremely readily (see Section IV, B, 5), and this reaction appears to take precedence over reduction, even in the presence of powerful reducing agents.^{126, 127} In dilute solution, however, epinochrome (**27**) was shown to take up two equivalents of hydrogen per mole, suggesting the initial formation of 5,6-dihydroxy-*N*-methylinndoline (**69**), i.e. the true leuco compound.¹⁶⁴ However, only traces of **69** were obtained on hydrogenation of **27** on a preparative scale; the main product isolated was the rearrangement product, i.e. 5,6-dihydroxy-*N*-methylinndole (**28**). On continued hydrogenation further reduction products of **28** were obtained.^{126, 127}



(69)

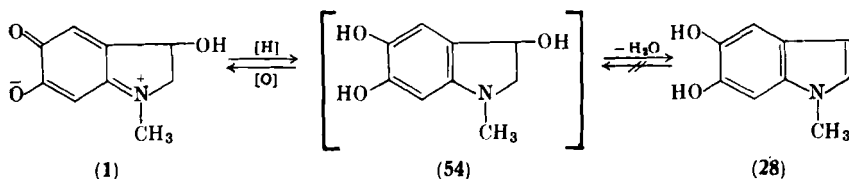
Rubreserine (**21**), the red oxidation product of eserine (physostigmine), is an interesting example of a compound with an aminochrome-type structure with no hydrogen atoms in the 3-position. It cannot, therefore, rearrange by the usual mechanism which involves the migration of a proton from the 3-position (see Section IV, B, 5), and consequently the reversible reduction of rubreserine (**21**) to leuco-rubreserine (**20**) has been known for many years^{101, 102} (see Section II, D, 2). The only other example reported so far of the isolation of a true leuco-aminochrome was that obtained by the reduction of 7-iododopachrome ethyl ester (**26**).¹⁰⁴ (This compound was probably erroneously described in the original reference as the 3-iodo derivative; cf. ref. 70) (see Section II, D, 2).

In all probability when adrenochrome (**1**) is reduced the initial product is 3,5,6-trihydroxy-*N*-methylinndoline (**54**) (i.e. the true "leuco-adrenochrome"). Polarographic studies have indicated that

¹⁶³ D. J. Bell, *Ann. Rept. Progr. Chem. (Chem. Soc. London)* **52**, 285 (1955).

¹⁶⁴ G. B. Koelle and J. S. Friedenwald, *Arch. Biochem. Biophys.* **32**, 370 (1951).

such a reaction probably does occur; although the initial product was formed reversibly, it rapidly decomposed irreversibly.^{164, 165} This latter process is the very rapid and irreversible dehydration of the 3-hydroxy-2,3-dihydropyrrole moiety of the indoline ring system in **54** to give 5,6-dihydroxy-*N*-methylindole (**28**). This reaction sequence presumably occurs under the influence of most reducing



agents except sodium bisulfite, which merely forms an addition product with adrenochrome (see Section IV, F). The other products present in reaction mixtures obtained from the action of various reducing agents on adrenochrome (and related aminochromes) are probably formed in one of the following ways: (i) as a result of the competing rearrangement reaction of the aminochromes, (ii) by the interaction of one of the primary products (e.g. **28**) with excess reducing agent or some oxidation product derived from the reducing agent, or (iii) by interaction of unreduced aminochrome with oxidized reducing agent, e.g. NaHSO_3 . In the case of the 7-halogenoaminochromes the above reactions are all complicated by the accompanying dehalogenation process to a greater or lesser extent.

The ingenious mechanism previously proposed⁶ to account for the products formed by the reduction of adrenochrome was based on two erroneous premises: first, that the hydrogenation of adrenochrome (**1**) stops after the addition of one atom of hydrogen per molecule of **1**, and second that the precursor of the adrenolutin (**31**) isolated when sodium hydrosulfite was the reducing agent was some hypothetical zwitterion isomeric with **1**. It has subsequently been shown that, in keeping with the polarographic evidence, two atoms of hydrogen are taken up per molecule of **1**, if a large quantity of a sufficiently active catalyst is used.¹⁶⁶ Compound **31** isolated from the products obtained on hydrogenation⁶ was probably formed by the intramolecular rearrangement of some **1** on the surface of the catalyst, which had simply acted as hydrogen-transfer agent.¹⁶⁶ The

¹⁶⁵ K. Wiesner, *Biochem. Z.* **313**, 48 (1942).

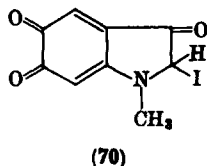
¹⁶⁶ J. Harley-Mason, private communication.

main non-ether-extractable product obtained when 1 was reduced with sodium hydrosulfite was, in fact, the adrenochrome-sodium bisulfite addition product.^{148, 155} Decomposition of this product with alkali regenerates free adrenochrome, which then undergoes the usual alkali-catalyzed rearrangement to 31 (cf. refs 3 and 148).

Relatively little work has been carried out on the reduction of the adrenochrome alkyl ethers, but it appears that they behave analogously to aminochromes with a 3-hydroxyl group.^{110, 155}

D. OXIDATION

No simple oxidation products of adrenochrome have been obtained in crystalline form. The evidence for and against the existence of oxoadrenochrome was summarized in an earlier review.³ Although the preparation of a substance described as 2-iodooxadrenochrome (70) by the oxidation of adrenaline with iodic acid was reported,^{87, 167} it was subsequently shown by an exhaustive consideration of its physical and chemical properties to be identical with 7-iodoadrenochrome (12)¹⁰⁹ (cf. ref. 70).



The aminochromes are intermediates in the formation of the dark pigments known as the melanins, i.e. the final products of catecholamine oxidation. However, aminochromes can be converted into melanins both by oxidative and non-oxidative processes (see Section V, A).

There are no reports in the literature of the formation of pyrrole derivatives by the oxidative degradation of the *o*-quinone rings of the simple aminochromes. However, several pyrrolecaboxylic acids have been obtained on oxidation of the melanins, which are considered by some authors to contain aminochrome units in the polymer (cf. ref. 168), (see Section V, A), and pyrrole-2,3,5-tricarboxylic acid has been

¹⁶⁷ E. Mácciotta, *Boll. Lab. Chim. Provinciali, (Bologna)* 6, No. 2, 49 (1955); *Chem. Abstr.* 50, 2368 (1956).

¹⁶⁸ R. A. Nicolaus, *Rass. Med. Sper.* 9, Suppl. No. 1, (1962).

obtained recently by the oxidation of betanidin (betanidin is the aglycone of the beet pigment betanin). Betanidin was considered to contain a dopachrome unit,¹⁶⁹ but very recent work has suggested that it contains a 5,6-dihydroxyindoline unit and not the corresponding aminochrome unit¹⁷⁰ (see Section VI, B, 1).

E. HALOGENATION

The aminochromes obtained on the oxidation of catecholamines with iodine or iodates are usually iodinated. These iodoaminochromes appear to be formed by a two-stage process, i.e. initial oxidation of the catecholamine to the simple aminochrome, followed by its iodination. (The evidence for such a two-stage process has been summarized previously.³) The very dark red crystalline solid isolated by Richter and Blaschko in 1937 from the oxidation of adrenaline with potassium iodate was formulated as the 2-iodo derivative of adrenochrome,⁶⁹ and at about the same time Green and Richter reported the preparation of a similar compound, described as 2-bromoadrenochrome, by the oxidation of adrenaline with bromine.¹⁴⁵ Although no proof was offered that halogenation of the aminochrome molecule occurred in the 2-position, this was accepted as a fact by most subsequent workers and all new iodoaminochromes were described as 2-iodo derivatives with the exception of a few that were equally erroneously described as 3-iodo derivatives¹⁰⁴ (cf. ref. 109). However, the fact that no unambiguous proof for 2-substitution existed was subsequently pointed out by Heacock.³ It has now been definitely established that halogenation occurs at the 7-position⁷⁰ and not at the 2- or 3-position as previously supposed.

The n.m.r. spectra of several 5,6-dihydroxyindoles (and their diacetyl derivatives) obtained by reduction of different non-halogenated aminochromes were compared with those obtained from the appropriate 5,6-dihydroxy-(or 5,6-diacetoxy)-iodoindoles produced by reduction of the corresponding iodoaminochromes. The n.m.r. data clearly demonstrated the presence of α - and β -protons in the indole nuclei (except in the case of the products derived from 2-methylnoradrenochrome and the corresponding iodoaminochrome,

¹⁶⁹ M. Piattelli and L. Minali, *Rend. Acad. Sci. Fis. Mat. (Soc. Naz. Sci. Napoli)* **29**, 80 (1962).

¹⁷⁰ H. Wyler, T. J. Mabry, and A. S. Dreiding, *Helv. Chim. Acta* **46**, 1745 (1963).

where there are no α -hydrogen atoms due to the 2-methyl substitution).⁷⁰ (The n.m.r. characteristics of the α - and β -protons in the indole nucleus have been previously studied in some detail by Cohen *et al.*¹⁷¹) If the original iodination had occurred in the 2-position, the reduction products of the iodoaminochromes mentioned above would have been 2-iodoindoles, and the signal due to the α -hydrogen should not have been present in the n.m.r. spectra of these particular compounds. The n.m.r. spectra of the 5,6-dihydroxyindoles derived from the uniodinated aminochromes clearly showed peaks due to aromatic protons in both the 4- and 7-positions; however, the peaks assigned to the 7-protons were absent from the spectra of the iodinated compounds.⁷⁰ Furthermore, the n.m.r. spectral characteristics of the protons on the *N*-alkyl group (if present) in the 5,6-dihydroxyindole showed a striking dependence on iodination; this would have been expected in the case of 7- but not 4-substitution.⁷⁰ Comparison of the n.m.r. spectra of the 3,5,6-triacetoxyindoles, obtained on acetylation and rearrangement of the aminochromes with acetic anhydride in pyridine, with the spectra of the 3,5,6-triacetoxyiodoindoles obtained in a similar manner from the corresponding iodoaminochromes, confirmed that iodination occurred in the 7-position.⁷⁰ Similar considerations apply to the derivatives of bromoadrenochrome; consequently, this aminochrome should be formulated as 7-bromoadrenochrome.⁷⁰

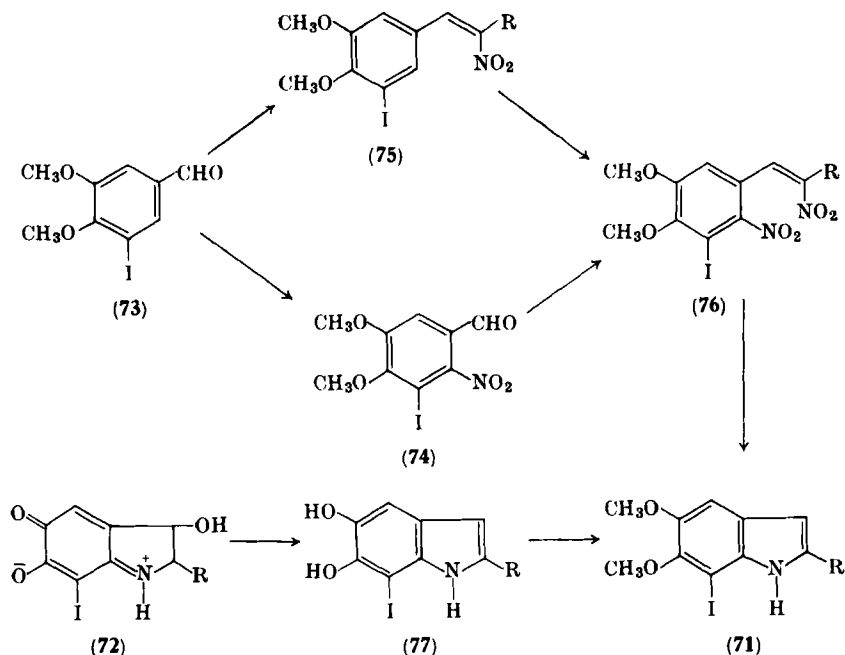
The position of the iodine atom in the aminochrome derivatives has been confirmed by the unambiguous synthesis of 7-iodo-5,6-dimethoxyindole (**71**; R = H) and 7-iodo-5,6-dimethoxy-2-methylindole (**71**; R = CH₃) and establishing the identity of these compounds with the dimethyl ethers of the 5,6-dihydroxyindoles obtained on reduction of 7-iodonoradrenochrome (**72**; R = H) and 7-iodo-2-methylnoradrenochrome (**72**; R = CH₃), respectively. 5-Iodoveratraldehyde (**73**) or its 6-nitro derivative (**74**)¹⁷² was condensed with nitromethane to give 5-iodo-3,4-dimethoxy- β -nitrostyrene (**75**; R = H) or 5-iodo-3,4-dimethoxy- β ,6-dinitrostyrene (**76**; R = H), respectively. This latter compound could also be obtained by the nitration of **75** (R = H). Reductive cyclization of **76** (R = H) with hydrogen in the presence of 10% palladium-charcoal gave a mixture of 7-iodo-5,6-dimethoxyindole (**71**; R = H), the corres-

¹⁷¹ L. A. Cohen, J. W. Daly, H. Kny, and B. Witkop, *J. Am. Chem. Soc.* **82**, 2184 (1960).

¹⁷² R. A. Heacock and O. Hutzinger, *J. Chem. Soc.* 3574 (1963).

ponding deiodinated indole derivative (5,6-dimethoxyindole), and, rather surprisingly, a trace of what was probably the corresponding 4-iodo derivative.⁷⁰

7-Iodo-5,6-dimethoxy-2-methylindole (**71**; R = CH₃) was prepared from **76** (R = CH₃) in an analogous manner.⁷⁰ Compounds **71** (R = H) and **71** (R = CH₃) were identical to the dimethyl ethers of the 5,6-dihydroxyiodoindoles (**77**; R = H or CH₃) obtained by reduction of **72** (R = H) or **72** (R = CH₃), respectively.⁷⁰



F. SODIUM BISULFITE ADDITION PRODUCT FORMATION

The red color of aminochrome solutions is rapidly discharged by the addition of sodium bisulfite with the formation of pale-yellow fluorescent solutions. The reactions of adrenochrome with sulfites and bisulfites have been the subject of several previous reports.^{12, 102, 109, 118, 119, 123, 128, 148, 152, 155, 158, 173-177} Although it was originally

¹⁷³ P. Bouvet, *Ann. Pharm. Franc.* **7**, 517 (1949).

¹⁷⁴ J. van Espen, *Pharm. Acta Helv.* **33**, 207 (1958).

¹⁷⁵ P. Bouvet, *Ann. Pharm. Franc.* **7**, 637 (1949).

¹⁷⁶ M. J. Oesterling and R. L. Tse, *Federation Proc.* **18**, 296 (1959).

¹⁷⁷ R. L. Tse and M. J. Oesterling, *Clin. Chim. Acta* **8**, 393 (1963).

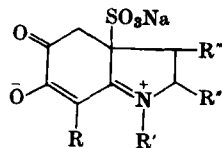
believed that adrenochrome was reduced to some form of leuco compound with sodium bisulfite,^{152, 158} it is now generally agreed that the interaction of an aminochrome with sodium bisulfite merely leads to the formation of an addition product (as was first suggested in 1949 by Bouvet).¹⁷³

Paper chromatographic examination of several aminochrome-sodium bisulfite reaction mixtures has shown that addition product formation seems to be general.¹⁵⁵ These products can easily be detected on paper chromatograms (see Table IX for R_f values), since they exhibit a pronounced yellow fluorescence in ultraviolet light.^{118, 119, 123, 148, 155, 174} Although the yellow fluorescence of the adrenochrome-sodium bisulfite addition compound could conceivably be mistaken for the fluorescence of adrenolutin, there are a number of important differences between the fluorescence characteristics of these two compounds. First, the maximum fluorescence of the adrenochrome-sodium bisulfite addition product is observed at excitation and emission wavelengths (i.e. excitation and fluorescence maxima occur at 355 and 465 m μ , respectively¹⁷⁸) different from those for maximal fluorescence of adrenolutin (i.e. 410–510 m μ); second, the fluorescence intensity of the complex is considerably weaker for a given quantity of compound.¹⁷⁸ However, due to the stability of the complex, the fluorescence of its solutions persists for several days.¹⁷⁸ The aminochrome-sodium bisulfite addition products react relatively slowly with typical indole color reagents such as Ehrlich's reagent, cinnamaldehyde, etc., but they do give characteristic colors quite rapidly with ferric chloride and ammoniacal silver nitrate.¹⁵⁵ The complexes are decomposed by alkali to the red aminochrome, which in turn is isomerized to the corresponding 5,6-dihydroxyindoxyl or 5,6-dihydroxyindole derivative.^{148, 155}

The 7-iodoaminochromes also form addition products with sodium bisulfite, although formation of these adducts usually appears to be accompanied by some deiodination, with the consequent formation of the corresponding deiodinated complexes.¹⁵⁵ The 7-iodonor-adrenochrome-sodium bisulfite addition product has been reported to be more stable in this respect (i.e. it shows less tendency to deiodinate) than the corresponding 7-iodoadrenochrome adduct.¹¹⁹ Although it has not proved possible to demonstrate effectively the presence of both the 7-iodoaminochrome complex and the corres-

¹⁷⁸ G. L. Mattok, D. Wilson, and R. A. Heacock, unpublished work (1962) and Abstracts (V), 6th Intern. Congr. Biochem., New York, 1964, p. 391.

TABLE IX

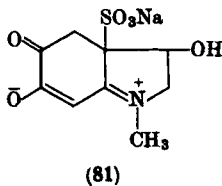
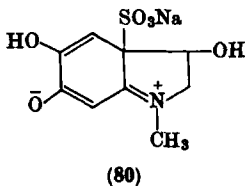
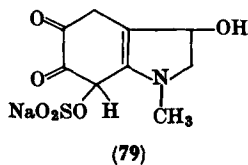
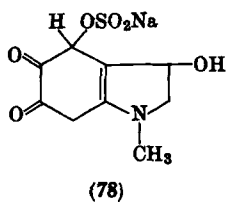
PAPER CHROMATOGRAPHIC DATA ON SOME AMINOCHROME-SODIUM BISULFITE ADDITION PRODUCTS^a

Aminochrome-NaHSO ₃ addition product	R	R'	R''	R'''	Solvent 1	<i>R_f</i> value ^{b, c} Solvent 2	Solvent 3
Noradrenochrome-NaHSO ₃	H	H	H	OH	93 ^d	—	4 ^d
Adrenochrome-NaHSO ₃	H	CH ₃	H	OH	93 ^d	88 ^{e, f}	4 ^{d, g}
<i>N</i> -Ethylnoradrenochrome-NaHSO ₃	H	C ₂ H ₅	H	OH	—	90 ^f	—
<i>N</i> -Isopropylnoradrenochrome-NaHSO ₃	H	<i>i</i> -C ₃ H ₇	H	OH	—	93 ^f	—
Adrenochrome methyl ether-NaHSO ₃	H	CH ₃	H	OCH ₃	—	90 ^f	—
Norepinochrome-NaHSO ₃	H	H	H	H	94 ^h	—	2 ^h
Dopachrome-NaHSO ₃	H	H	COOH	H	98 ^h	—	0.6 ^h
7-Iodonoradrenochrome-NaHSO ₃ ⁱ	I	H	H	OH	93 ^d	—	6 ^d
7-Iodoadrenochrome-NaHSO ₃ ⁱ	I	CH ₃	H	OH	93 ^d	—	—

^a Probable structure shown in the structural formula [cf. R. L. Tse and M. J. Oesterling, *Clin. Chim. Acta* **8**, 393 (1963)].^b *R_f* value $\times 100$.^c Solvent 1 = distilled water; Solvent 2 = 2% aqueous acetic acid; Solvent 3 = *n*-butanol-acetic acid-water (78:17:5).^d S. Bouchilloux, *Compt. Rend. Soc. Biol.* **153**, 1818 (1959).^e R. A. Heacock and B. D. Laidlaw, *Chem. Ind. (London)* 1510 (1958).^f R. A. Heacock and B. D. Scott, unpublished work (1960-1962).^g J. van Espen, *Pharm. Acta Helv.* **33**, 207 (1958).^h S. Bouchilloux and A. Kodja, *Bull. Soc. Chim. Biol.* **42**, 65 (1960).ⁱ It has recently been shown that the iodoaminochromes should be formulated as 7-iodo derivatives [R. A. Heacock, O. Hutzinger, B. D. Scott, J. W. Daly, and B. Witkop, *J. Am. Chem. Soc.* **85**, 1825 (1963)]; consequently, all such compounds are described in this manner throughout this review.

ponding iodine-free derivative in mixtures by paper chromatography, satisfactory separations of these two complexes have been achieved by paper electrophoresis.¹¹⁹ Several years earlier Bouvet had shown that the 7-iodoadrenochrome-sodium bisulfite addition product gave adrenochrome, and not 7-iodoadrenochrome, on cautious decomposition with alkali.^{173, 175} Paper chromatography of several different aqueous 7-iodoaminochrome-sodium bisulfite reaction mixtures showed that, in addition to the expected addition products, small quantities of other unidentified substances were formed in each case, including one which, from its color reactions, appeared to be an indoline derivative.¹⁵⁵ This product was also probably sulfur-free since traces of it were detected chromatographically among the products obtained from the same aminochromes with other reducing agents (e.g. zinc and dilute acetic acid).¹⁵⁵

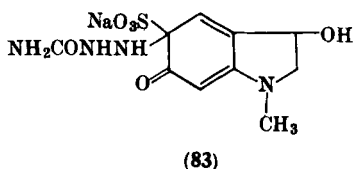
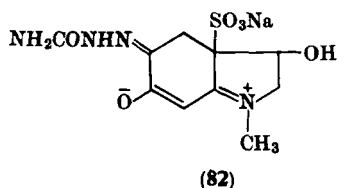
The adrenochrome-sodium bisulfite addition product has been isolated as a stable pale-yellow crystalline solid.^{174, 177, 178} It was originally postulated by Bouvet that addition of the sodium bisulfite molecule occurred at one or both of the *o*-quinonoid carbonyl groups in the adrenochrome molecule¹⁷³; subsequently it was suggested by van Espen that the bisulfite residue was attached at either the 4- or 7-position in the 6-membered ring¹⁷⁴ (i.e. **78** or **79**). Structures of this type involving C—O—S linkages are unlikely, and recently Tse and Oesterling suggested that 1,4-addition of the sodium bisulfite molecule occurs across the α,β -unsaturated C-5 carbonyl system of adrenochrome (**1**) giving a structure of type **80** or **81**.¹⁷⁷ The former



structure was said to predominate in solution and the latter in the solid state.¹⁷⁷

The ultraviolet spectrum of aqueous solutions of the adrenochrome-sodium bisulfite addition product has maxima at 348 and 245 $m\mu$.^{128, 174, 177} The infrared spectrum (KBr disc)¹⁷⁷ of the addition complex shows, according to Tse and Oesterling, a single carbonyl peak at 1725 cm^{-1} , attributed to the C-5 carbonyl group, and peaks at 1630 and 1600 cm^{-1} attributed to the vinylogous amide system, which includes the ionized C-6 carbonyl group.¹⁷⁷ The spectrum has also been measured as a Nujol mull.¹⁷⁸ In this case a sharp peak at 3340 cm^{-1} due to the 3-hydroxyl group was observed.¹⁷⁸ Peaks in the "carbonyl" region were observed at 1722, 1630, and 1575 cm^{-1} in the Nujol spectrum.¹⁷⁸ (The spectrum in this region was very similar to that of adrenochrome; cf. ref. 108.) The strong absorption at 1575 cm^{-1} was probably due to the ionized carbonyl group at C-6, and the 1722 and 1630 cm^{-1} peaks could be assigned to the C-5 carbonyl and the $>C=N^+$ groups, respectively.¹⁷⁸

The sodium bisulfite addition compounds must have a free (or potentially free) "ketone-type" carbonyl group, since they readily form derivatives with typical ketone reagents such as semicarbazide and 2,4-dinitrophenylhydrazine.¹⁷⁴ Decomposition of these derivatives with alkali gives the corresponding adrenochrome derivatives; e.g., adrenochrome monosemicarbazone would be obtained from the semicarbazone of the adrenochrome-sodium bisulfite complex.¹⁷⁴ If one accepts Tse and Oesterling's formulation of the adrenochrome-sodium bisulfite complex, the semicarbazone would probably have a basically similar structure (i.e. **82**). This type of structure is more

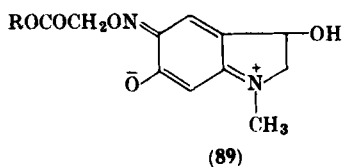
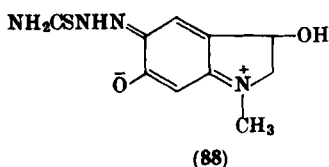
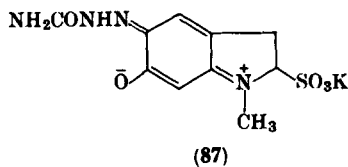
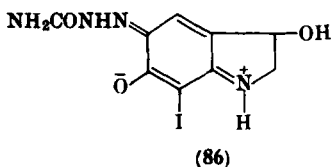
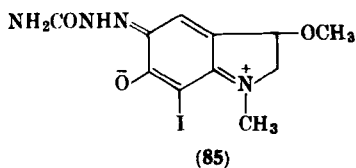
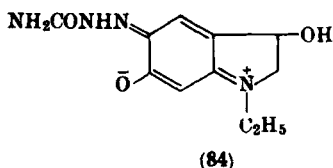


likely than that previously proposed (**83**) in the patent literature for products obtained from the interaction of the adrenochrome-sodium bisulfite addition product and semicarbazide¹⁷⁹ or similar "carbonyl" reagents¹⁷⁹ (see Section IV, G).

¹⁷⁹ Société Belge de l'Azote et des produits chimiques du Marly S. A., Belgian Patent 510,295 (1952); *Chem. Abstr.* **48**, 3397 (1954).

G. CONDENSATION PRODUCT FORMATION

One of the most characteristic reactions of the aminochromes is the ready formation of mono-derivatives with typical ketone reagents, e.g. semicarbazide, phenylhydrazine, etc. A relatively large number of derivatives of this nature have been prepared because of their reported hemostatic activity (cf. refs. 2 and 3). Compounds of this type that had been described in the literature prior to December 1959 are listed in a previous review (Heacock³). Some further examples of this class of compounds have been described recently. They are *N*-ethylnoradrenochrome semicarbazone (84) (orange-red needles, m.p.¹⁸⁰ 215°)⁶⁵; 7-iodoadrenochrome methyl ether semicarbazone



(85) (cherry-red prisms, m.p. 150°)⁷⁰, 7-iodonoradrenochrome semicarbazone (86) (deep red prisms, m.p. 143–148°)¹⁸¹, 2-methyladrenochrome semicarbazone (m.p. 222°),¹⁸¹ 2-methyl-*N*-ethylnoradrenochrome semicarbazone (m.p. 213–214°),¹⁸¹ potassium epinochrome-2-sulfonate semicarbazone (87) (orange needles, m.p. 300°),¹⁸² and

¹⁸⁰ All these compounds melt with decomposition.

¹⁸¹ R. A. Heacock and B. D. Scott, unpublished work (1962).

¹⁸² J. Iwao and K. Tomino, U. S. Patent 2,950,287 (1960); *Chem. Abstr.* **55**, 2687 (1961).

adrenochrome thiosemicarbazone (88) (m.p. 220°).¹⁸³ The thiosemicarbazone has previously been described in the patent literature.¹⁸⁴ A number of interesting compounds of the type depicted in structural formula 89, derived from adrenochrome and derivatives of aminoxyacetic acid, have been described recently, where R may be the cation derived from the alkali metals, ammonia, or certain organic bases.¹⁸⁵ The free acid (89; R = H) was reported to have a melting point between 123 and 127°.¹⁸⁵

In attempts to increase the water solubility of compounds of this general type for pharmaceutical purposes, the effects of several additives on their water solubility have been studied; the alkali metal salicylates are quite effective in raising the solubility of adrenochrome monosemicarbazone.¹⁸⁶ The solubilizing action of a number of aromatic and heterocyclic amides on adrenochrome monosemicarbazone has also been reported^{187, 188}; *N*-2-pyridylnicotinamide has about three times the solubilizing action of nicotinamide on adrenochrome monosemicarbazone.¹⁸⁷ The semicarbazone and oxime of adrenochrome are also rendered more soluble in water by the addition of sodium 4-aminonaphthalenesulfonate or its *N*-acetyl derivative.¹⁸⁹

The ultraviolet and visible spectroscopy of adrenochrome monosemicarbazone has been described adequately in previous reviews; cf. refs. 2 and 3. Essentially, neutral solutions of aminochrome monosemicarbazones show a maximum in the region 354–357 m μ and a broad flat inflection in the region 400–440 m μ (see refs. 2 and 3 for references). In acid solution a slight shift of the 354–357 m μ peak towards longer wavelengths is observed. However, at alkaline pH the 354–357 m μ peak disappears and the inflection in the 400–440 m μ region is replaced by a maximum in the 437–450 m μ region¹⁹⁰ (cf.

¹⁸³ P. W. Sadler, *J. Chem. Soc.* 243 (1961).

¹⁸⁴ D. Fleischhaker and N. Barsel, U. S. Patent 2,712,024 (1955); *Chem. Abstr.* **50**, 5747 (1956).

¹⁸⁵ D. Fleischhaker and N. Barsel, U. S. Patent 3,006,924 (1961); *Chem. Abstr.* **56**, 2428 (1962).

¹⁸⁶ D. Fleischhaker and N. Barsel, U. S. Patent 2,581,850 (1952); *Chem. Abstr.* **46**, 2759 (1952).

¹⁸⁷ M. Samejima, *Yakugaku Zasshi* **80**, 1706 (1960); *Chem. Abstr.* **55**, 10439 (1961).

¹⁸⁸ M. Samejima, *Yakugaku Zasshi* **80**, 1719 (1960); *Chem. Abstr.* **55**, 10440 (1961).

¹⁸⁹ R. Ruis Garriga, Spanish Patent 242,506 (1958); *Chem. Abstr.* **55**, 25174 (1961).

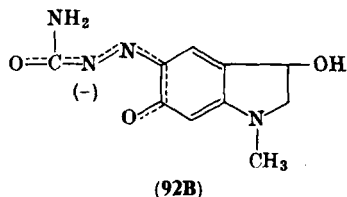
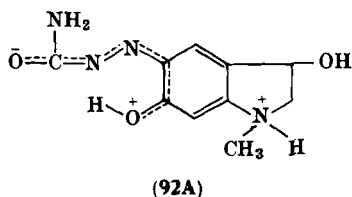
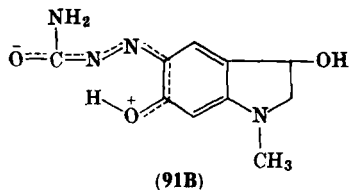
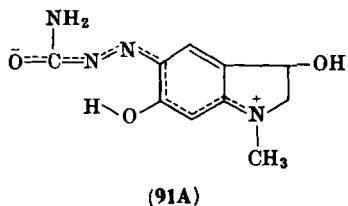
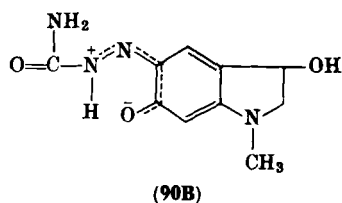
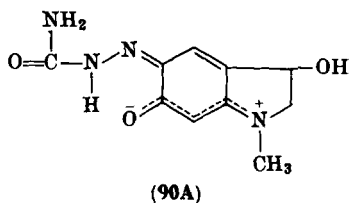
¹⁹⁰ F. Ramirez and P. von Ostwalden, *J. Org. Chem.* **20**, 1676 (1955).

refs. 2 and 3). Other aminochrome derivatives of this type show similar spectroscopic shifts with changes in pH. The 2,4-dinitrophenylhydrazones of adrenochrome, dopachrome, and norepinephrine have maxima in the region 450–456 $m\mu$, with shoulders at ca. 391 $m\mu$ in acid solution, but under alkaline conditions their spectra show maxima in the 580–598 $m\mu$ region with shoulders at ca. 460 $m\mu$.^{77, 78}

The syntheses of the monoxime [mono- or di-hydrate, m.p. 178° (decomp.)] and monosemicarbazone [m.p. 223° (decomp.)] of DL-adrenochrome have recently been described by Remizov.¹⁹¹ The majority of previous publications referring to these compounds have dealt with derivatives of adrenochrome prepared initially from L-adrenaline. The picrates obtained from the DL-oxime and DL-semicarbazone of adrenochrome were described as yellow powders, decomposing at 124 and 150°, respectively.¹⁹¹ Remizov also described the formation of highly colored complexes from the interaction of the DL-oxime and DL-semicarbazone with certain metal ions (e.g. Co^{++} , Ni^{++} , Cr^{+++} , Fe^{++} , and Fe^{+++}).¹⁹¹

Two possible cross-conjugated resonance interactions are possible in the adrenochrome monosemicarbazone (90) molecule. Interactions of the *m*-amino-*o*-quinone type (90A) and the *o*-quinone semicarbazone type (90B) would account for the lack of normal carbonyl reactivity associated with the C-6 carbonyl group and the weak basicity of the heterocyclic nitrogen atom.¹⁹⁰ Tautomeric forms can also be written for 90A and 90B representing the corresponding *o*-azophenol structures, i.e. 91A and 91B. In acid solution (pH 1.1) the adrenochrome monosemicarbazone cation (which can be written as 92A) is probably responsible for the absorption maximum at 377 $m\mu$.¹⁹⁰ In strongly alkaline solution (pH 13) the anionic form (92B) is responsible for the 447 $m\mu$ absorption peak.¹⁹⁰ Isosbestic points are observed at 360 and 393 $m\mu$, the former representing the equilibrium between the cationic and neutral forms and the latter the equilibrium between the neutral and anionic forms.¹⁹⁰ It is of interest to note that no spectral changes with increasing pH are observed for the *N*-methylsemicarbazone since in this case there is no proton on N-2 available to migrate.² The above explanation of the spectral changes associated with variation of the pH of solutions of adrenochrome monosemicarbazone¹⁹⁰ is somewhat more plausible than that offered by Remizov.¹⁹¹

¹⁹¹ A. L. Remizov, *Zh. Obshch. Khim.* **28**, 3338 (1958); *Chem. Abstr.* **53**, 14038 (1959).



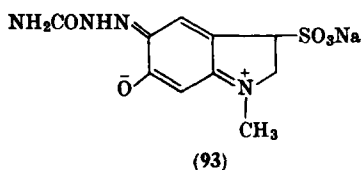
Addition products have been obtained from aminochrome derivatives such as the semicarbazone, with sodium bisulfite. Recently Correia Alves reported the preparation of a compound described as "adrenochrome semicarbazone sodium sulfonate" (m.p. $> 300^\circ$) by treating a solution of adrenochrome monosemicarbazone (90) in sodium carbonate solution with sulfur dioxide at 40° for several days¹⁹²; this compound was apparently different from the substance (m.p. $227-228^\circ$) obtained in a somewhat similar manner by Iwao^{193, 194} and may be comparable to the compound (83) (m.p. $> 300^\circ$) previously described in a Belgian patent¹⁷⁹ (see Section IV, F). Iwao established the structure of his compound as the sodium salt of epinochrome-3-sulfonic acid monosemicarbazone (93).¹⁹³

The products obtained from the interaction of adrenochrome monosemicarbazone and amine bisulfites have been described; e.g.,

¹⁹² A. Correia Alves, *Anais Fac. Farm. Porto* **21**, 11 (1961); *Chem. Abstr.* **59**, 544 (1963).

¹⁹³ J. Iwao, *Pharm. Bull. (Tokyo)* **4**, 251 (1956).

¹⁹⁴ J. Iwao, K. Tomino, and M. Kawazu, Japanese Patent 7,781 (1957); *Chem. Abstr.* **52**, 13802 (1958).



90 gives a product melting at 196° on treatment with triethylamine bisulfite at 40° for 3 hours. Similar products were obtained from **90** with ethanolamine, pyridine, and nicotinamide.¹⁹⁵

H. REACTION WITH ETHYLENEDIAMINE

The formation of relatively stable fluorescent products by the reaction of adrenaline with ethylenediamine (and certain other primary amines) in air, first reported in 1948 by Natelson *et al.*,¹⁹⁶ was adapted by Weil-Malherbe and Bone in 1952 for the assay of catecholamines.^{197, 198} Since 1952 much work, largely of an empirical nature, has been carried out to improve the analytical procedure since often apparently minor variations of the reaction conditions have a significant effect on the fluorescence observed (see Section V, E, 4). Paper chromatographic examination of the reaction mixtures obtained from adrenaline and noradrenaline suggested that more than one product could be formed in each case.¹⁹⁹⁻²⁰⁵ The main fluorescent product of the interaction of adrenochrome (**1**) (obtained by oxidation of adrenaline) and ethylenediamine in air has been obtained as a crystalline solid by Harley-Mason and Laird and shown to be 2,3-dihydro-3-hydroxy-1-methylpyrrolo[4,5-g]quinoxaline (**94**) (7% yield).^{206, 207} This compound has two hydrogen atoms less than

¹⁹⁵ M. Sumi, Japanese Patent 347 (1960); *Chem. Abstr.* **54**, 21130 (1960).

¹⁹⁶ S. Natelson, J. K. Logovoy, and J. B. Pincus, *Arch. Biochem.* **23**, 157 (1949).

¹⁹⁷ H. Weil-Malherbe and A. D. Bone, *Biochem. J.* **51**, 311 (1952).

¹⁹⁸ H. Weil-Malherbe and A. D. Bone, *Lancet* (1) 974 (1953).

¹⁹⁹ G. P. Burn and E. O. Field, *Nature* **178**, 542 (1956).

²⁰⁰ J. G. Young and R. L. Fischer, *Science* **127**, 1390 (1958).

²⁰¹ K. Yagi and T. Nagatsu, *Nature* **183**, 822 (1959).

²⁰² G. Nadeau and L.-P. Joly, *Nature* **182**, 180 (1958).

²⁰³ L.-P. Joly and G. Nadeau, *Nature* **184**, 1483 (1959).

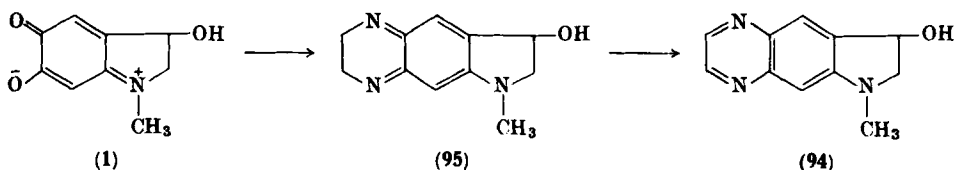
²⁰⁴ K. Yagi, T. Nagatsu, and I. Nagatsu, *Nature* **186**, 310 (1960).

²⁰⁵ K. Yagi and T. Nagatsu, *J. Biochem. (Tokyo)* **48**, 439 (1960).

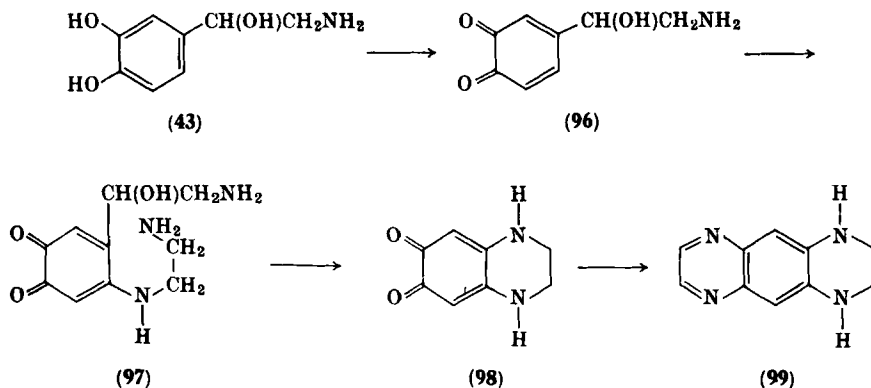
²⁰⁶ J. Harley-Mason and A. H. Laird, *Biochem. J.* **69**, 59P (1958).

²⁰⁷ J. Harley-Mason and A. H. Laird, *Tetrahedron* **7**, 70 (1959).

the structure (95) originally proposed for the fluorescent substance by Weil-Malherbe and Bone.¹⁹⁷ However, the product obtained from noradrenaline (43) was shown by Harley-Mason and Laird to be



1,2,3,4-tetrahydro-1,4,5,8-tetraazaanthracene (99),^{206, 207} identical with the product obtained from catechol under the same conditions. These authors explained the formation of this product in the following manner: the intermediate "noradrenaline-quinone" (96) (i.e. the initial oxidation product of noradrenaline), which presumably cyclizes more slowly than the analogous "adrenaline-quinone" (see



Section II, C), is attacked by an ethylenediamine unit before it cyclizes to form noradrenochrome. The intermediate (97) then cyclizes with elimination of the original side chain forming the *o*-quinone (98), which subsequently condenses with another molecule of ethylenediamine to give the final product, i.e. 99.²⁰⁷ The product (99) was also readily obtained by the reaction of 2,5-dihydroxybenzoquinone with ethylenediamine in hot aqueous solution in air.²⁰⁷ It was further shown that other catecholamines with a hydroxyl group *alpha* to the benzene ring and a secondary amino group in the side chain (e.g. *N*-isopropylnoradrenaline) gave compounds similar

to **94**.²⁰⁷ Other 4-substituted catechols (other than the adrenaline type) with an *alpha* side-chain hydroxyl group (e.g. 3,4-dihydroxymandelic acid) also gave **99**.²⁰⁷ 4-Substituted catechols without an *alpha* side-chain hydroxyl group (e.g. 4-methylcatechol and 3,4-dihydroxyphenylethylamine) gave a mixture of different fluorescent products, since elimination of the side chain by a retro-aldol condensation was not possible in this case.²⁰⁷ Solutions of **99** were sensitive to light and the fluorescence faded on illumination of the solution,²⁰⁷ explaining the findings of Goldfien and Karler that the noradrenaline assay procedure was light sensitive.²⁰⁸ Weil-Malberbe has pointed out that the divergencies in the paper chromatographic results reported by several workers may have been due to the various investigators using widely differing reaction conditions, some of which were quite different from the conditions employed in the original assay procedure.²⁰⁹ Weil-Malberbe further showed that when the products obtained from reactions between adrenaline, noradrenaline, catechol, and 3,4-dihydroxymandelic acid with ethylenediamine (carried out as close as possible to the assay conditions) were examined fluorimetrically and paper chromatographically, essentially only one product was obtained from adrenaline, but the same two different products were obtained from the other catechol derivatives.²⁰⁹ The similarity of the products obtained by this general procedure from catechol, noradrenaline, and 3,4-dihydroxymandelic acid has also been reported by Nagatsu and Yagi.²¹⁰

V. Some Comments on the Significance of Aminochrome Chemistry to Biology and Medicine

A. MELANIN FORMATION

The importance of the aminochromes as intermediates in the formation of the dark colored pigments known as melanins, in plants and animals, has been recognized for many years. In fact, it was during the course of his investigations into the chemistry of melanogenesis, nearly forty years ago, that Raper essentially correctly formulated the red pigment dopachrome (i.e. an aminochrome) formed as an intermediate during melanogenesis from DOPA.⁷²

²⁰⁸ A. Goldfien and R. Karler, *Science* **127**, 1292 (1958).

²⁰⁹ H. Weil-Malherbe, *Biochim. Biophys. Acta* **40**, 351 (1960).

²¹⁰ T. Nagatsu and K. Yagi, *Nature* **193**, 484 (1962).

The subsequent developments and modifications of Raper's ideas have been extensively covered in publications by several investigators, e.g. Raper,²¹¹ Lerner,^{33, 212} Mason,^{34, 216, 217} Fox,²¹³ Thomas,²¹⁴ and Cromartie and Harley-Mason.²¹⁵ However, recent authors have suggested that Raper's original scheme may involve a considerable oversimplification of the problem (e.g. Nicolaus¹⁶⁸ and Swan²¹⁸). The mode of formation of the aminochromes by the oxidation of catecholamines is described in Section II. The subsequent transformation of the aminochromes into melanins occurs by more complex processes. It has been generally accepted in the past that rearrangement of the aminochrome to a 5,6-dihydroxyindole was an essential preliminary step in melanogenesis, but recent work has suggested that distinct aminochrome units (derived from DOPA and dopamine) may be incorporated directly into the melanin polymer.^{168, 218-221}

5,6-Dihydroxyindole and 5,6-dihydroxyindole-2-carboxylic acid were shown to form after the red pigment stage that occurred during the conversion of DOPA into a melanin, by Raper, who isolated these compounds as their dimethyl ethers.⁷² The presence of 5,6-dihydroxyindoles in solutions of DOPA, dopamine, and noradrenaline which are undergoing oxidation has subsequently been confirmed by paper and thin-layer chromatography.^{118, 120, 222} 5,6-Dihydroxyindole and 5,6-dihydroxyindole-2-carboxylic acid have recently been isolated from the alkali fusion products of sepiomelanin, indicating

²¹¹ H. S. Raper, *J. Chem. Soc.* 125 (1938).

²¹² A. B. Lerner and T. B. Fitzpatrick, *Physiol. Rev.* **30**, 91 (1950).

²¹³ D. L. Fox, "Animal Biochromes and Structural Colours," p. 215. Cambridge University Press, Cambridge, 1953.

²¹⁴ M. Thomas, in "Modern Methods of Plant Analysis" (K. Peach and M. V. Tracey, eds.), Vol. IV, p. 661. Springer-Verlag, Berlin, 1955.

²¹⁵ R. I. T. Cromartie and J. Harley-Mason, *Biochem. J.* **66**, 713 (1957).

²¹⁶ H. S. Mason, *Advan. Enzymol.* **19**, 79 (1957).

²¹⁷ H. S. Mason, in "Pigment Cell Biology" (M. Gordon, ed.) p. 563. Academic Press, New York, 1959.

²¹⁸ G. A. Swan, *Ann. N. Y. Acad. Sci.* **100**, 1005 (1963).

²¹⁹ R. A. Nicolaus, M. Piattelli, and G. Narni, *Rend. Accad. Sci. Fis. Mat. (Soc. Naz. Sci. Napoli)* **27**, 1 (1960).

²²⁰ M. Piattelli and R. Nicolaus, *Rend. Accad. Sci. Fis. Mat. (Soc. Naz. Sci. Napoli)* **27**, 499 (1960).

²²¹ M. Piattelli and R. A. Nicolaus, *Tetrahedron* **15**, 66 (1961).

²²² M. Piattelli, E. Fattorusso, and S. Magno, *Rend. Accad. Sci. Fis. Mat. (Soc. Naz. Sci. Napoli)* **28**, 168 (1961).

that such units are also definitely incorporated into the overall melanin structure.^{223, 224}

Bu'Lock has recently reported that in the formation of melanin by the oxidation of 5,6-dihydroxyindole, an intermediate compound, with an absorption maximum at 530 m μ , probably a 5,6-dihydroxyindolyindole-5,6-quinone, may represent an initial transient dimeric stage.²²⁵ (The reduced form of this compound, presumably a 5,6,5',6'-tetrahydroxydiindolyl, had a characteristic blue-violet fluorescence.²²⁵) The next stage in the melanogenesis was characterized by a compound with a flat absorption maximum at *ca.* 540 m μ . This was probably an oligomer of intermediate molecular weight, which eventually underwent further polymerization. Possibly the products that Bouchilloux and Kodja detected paper-chromatographically¹¹⁸ in aqueous solutions of 5,6-dihydroxyindole exposed to air (*R_f*'s in water of 0.0 and 0.50, with mauve and blue-green fluorescence, respectively) are comparable to products observed by Bu'Lock, particularly since traces of the fluorescent tetrahydroxydiindolyl are apparently present in melanizing solutions of 5,6-dihydroxyindole.²²⁵

It is interesting to note that there are several references in the patent literature to the use of 5,6-dihydroxyindoles in hair dyeing preparations.²²⁶⁻²²⁸

The non-oxidative formation of melanin from adrenochrome in acid solution, reported by Harley-Mason,⁶ has recently been shown by Bu'Lock to be controlled by a second-order reaction between adrenochrome and acid.¹⁰⁷ It was suggested that the initial product (not isolated) was probably 1-methylindole-5,6-quinone, which polymerized rapidly to melanin via dimers and oligomers.¹⁰⁷ (The intermediate monomer quinone also gave a melanin-like copolymer with indole.¹⁰⁷)

²²³ M. Piattelli, E. Fattorusso, S. Magno, and R. A. Nicolaus, *Rend. Accad. Sci. Fis. Mat. (Soc. Naz. Sci. Napoli)* **29**, 57 (1962).

²²⁴ M. Piattelli, E. Fattorusso, S. Magno, and R. A. Nicolaus, *Rend. Accad. Sci. Fis. Mat. (Soc. Naz. Sci. Napoli)* **29**, 153 (1962).

²²⁵ J. D. Bu'Lock, *Arch. Biochem. Biophys.* **91**, 189 (1960).

²²⁶ Société Monsavon-l'Oréal, German Patent 1,083,505 (1960); *Chem. Abstr.* **55**, 22726 (1961).

²²⁷ Société Monsavon-l'Oréal, British Patent 797,174 (1958); *Chem. Abstr.* **53**, 4665 (1959).

²²⁸ Société Monsavon-l'Oréal, British Patent 823, 503 (1959); *Chem. Abstr.* **54**, 7081 (1960).

B. AMINOCHROME FORMATION AS A POSSIBLE MINOR PATHWAY FOR CATECHOLAMINE METABOLISM

Since certain aminochromes (e.g. dopachrome) are essential intermediates in the process of melanogenesis (see preceding section) and in view of the widespread distribution of melanitic pigments in both the plant and animal kingdoms, it would appear, that in this respect at least, aminochromes must presumably be formed *in vivo* from certain of the catecholamines.

Although the two major routes for metabolism of adrenaline and noradrenaline are well established, and involve either methylation of the 3-hydroxyl group on the aromatic nucleus or oxidative deamination (cf. refs. 35, 93, 94, 229–231), the evidence to date does not warrant the complete rejection of a further possible metabolic pathway involving oxidation to an aminochrome (such as adrenochrome or noradrenochrome) in some instances.

Progress in establishing whether or not such a pathway exists, in the mammalian metabolism of adrenaline, has been handicapped to some extent by the controversy that developed over the reported presence of adrenochrome in human blood. A fluorimetric method reported for the assay of adrenochrome in human blood,²³² based on similar, previously reported, procedures,^{153, 233} involving isomerization of any adrenochrome present to adrenolutin by a zinc acetate-ascorbic acid mixture prior to reading the fluorescence was criticized by a number of authors,^{234–237} particularly on the basis of high and unstable blank readings.^{234, 237} A modification of the original controversial method, which involved replacement of the ascorbic acid by trichloroacetic acid, a procedure claimed by the authors to stabilize the blank fluorescence values,²³⁸ appears to have been overlooked by the critics of the original procedure.

²²⁹ J. Axelrod, "The Fate of Adrenaline and Noradrenaline, A Ciba Foundation Symposium on Adrenergic Mechanisms," p. 28. Churchill, London, 1960.

²³⁰ E. A. Zeller, *Pharmacol. Rev.* **11**, 387 (1959).

²³¹ E. Iisalo, *Acta Pharmacol. Toxicol.* **19**, Suppl. 1 (1962).

²³² A. N. Payza and M. E. Mahon, *Anal. Chem.* **31**, 1170 (1959).

²³³ D. Kertesz, *Bull. Soc. Chim. Biol.* **35**, 1157 (1953).

²³⁴ A. Feldstein, *Am. J. Psychiat.* **116**, 454 (1959).

²³⁵ S. Szara, J. Axelrod, and S. Perlin, *Am. J. Psychiat.* **115**, 162 (1958).

²³⁶ D. S. Layne and T. L. Sourkes, *J. Nervous Mental Disease* **130**, 93 (1960).

²³⁷ A. Randrup and I. Munkvad, *Am. J. Psychiat.* **117**, 153 (1960).

²³⁸ A. N. Payza and M. E. Mahon, *Anal. Chem.* **32**, 17 (1960).

Several different mammalian enzyme systems capable of oxidizing catecholamines to aminochromes have been described recently. The presence of an enzyme system in rabbit heart capable of oxidizing adrenaline "via the quinonoid pathway" has been reported^{44, 239}; Kaliman and Koshlyak detected similar enzyme systems in several of the tissues and organs of white rats.⁴⁵ Van der Wende and Spoerlein recently reported the oxidation of dopamine to melanin by a rat-brain enzyme⁴³; the same enzyme system oxidized adrenaline to a red pigment, presumably adrenochrome.⁴³ Axelrod has also recently established the existence of an enzyme system in the salivary gland of cats capable of oxidizing adrenaline to adrenochrome.²⁴⁰

Finally, evidence in support of the possibility of aminochrome formation *in vivo* is present in several publication. referring to the excretion of "aminochromes" (or closely related substances) in human urine.²⁴¹⁻²⁴⁵

C. ADRENOCROME METABOLISM

Noval *et al.* have recently shown that administration of adrenochrome to rats results in the appearance of three metabolites in the urine,¹¹⁶ which are probably sulfate esters of adrenolutin and 5,6-dihydroxy-*N*-methylindole (**28**); the strongly fluorescent conjugate from adrenolutin is relatively unstable.¹¹⁶ Administered adrenolutin appeared to form a similar unstable fluorescent conjugate in the rat, and the same two non-fluorescent sulfate esters of **28** were obtained from administered **28** as were obtained *in vivo* from adrenochrome. These findings are basically similar to those previously reported by Fischer and Lecomte,¹⁵³ although the earlier workers also reported that in cats and dogs some administered adrenochrome was excreted unchanged, while in rabbits the main product was adrenolutin (free and as a sulfate ester).¹⁵³ Schayer and

²³⁹ A. M. Utevsii and V. O. Osinskaya, *Ukr. Biokhim. Zh.* **27**, 401 (1955); *Chem. Abstr.* **50**, 1948 (1956).

²⁴⁰ J. Axelrod, *Biochim. Biophys. Acta* **85**, 247 (1964).

²⁴¹ H. Kaufmann and E. Koch, *Arch. Maladies Coeur Vaisseaux* **1**, 290 (1959).

²⁴² E. Koch and H. Kaufmann, *Bull. Soc. Chim. Biol.* **41**, 1565 (1959).

²⁴³ E. Kochová, *Biochem. Pharmacol.* **12**, Suppl. p. 178 (1963).

²⁴⁴ R. L. Veech, M. D. Altschule, H. Sulkowitch, and P. D. Holliday, *Arch. Gen. Psychiat.* **3**, 642 (1960).

²⁴⁵ R. L. Veech, L. B. Bigelow, W. Donner Denckla, and M. D. Altschule, *Arch. Gen. Psychiat.* **5**, 127 (1961).

Smiley demonstrated chromatographically the presence of an unstable yellow pigment in the urine of rats to which labeled adrenochrome had been administered.²⁴⁶ It now appears likely that extensive decomposition of this pigment occurred during the chromatographic process (cf. ref. 116).

D. PHYSIOLOGICAL ACTIVITY OF THE AMINOCHROMES

A detailed consideration of the many and diverse forms of physiological and psychological activity attributed to the aminochromes in general, and adrenochrome in particular, is outside the scope of this review. However, references 2, 32, and 247–249 will serve as a guide to further reading on the subject.

E. CATECHOLAMINE ASSAY PROCEDURES

1. Introduction

The vast majority of the chemical methods in widespread use for the assay of catecholamines involve, after extraction of the catecholamines from the biological system in question, their oxidation to aminochromes, which can then be determined directly by colorimetry or, after conversion into suitable derivatives, by fluorimetry. In general, colorimetric techniques based simply on aminochrome formation are not sufficiently sensitive for accurate determination of adrenaline and noradrenaline in body fluids and tissues, except in the case of certain pathological conditions. Such procedures are usually sensitive enough, however, for the assay of pharmaceutical preparations. The formation of suitable fluorescent derivatives usually involves either (i) the alkaline rearrangement of the aminochromes to so-called "lutins" (i.e. 5,6-dihydroxyindoxyl derivatives) (see Section IV, B) or (ii) the reaction of the catecholamine oxidation products with ethylenediamine. The latter procedure does not involve a distinct oxidation stage, although some degree of oxidation of the catecholamines is an essential prerequisite for the formation of fluorescent derivatives, and this is presumably brought about by atmospheric oxygen (see Section IV, H).

²⁴⁶ R. W. Schayer and R. L. Smiley, *J. Biol. Chem.* **202**, 425 (1953).

²⁴⁷ B. Kisch, *Exptl. Med. Surg.* **5**, 166 (1947).

²⁴⁸ K. Tatai, *Seitai No Kagaku* **7**, 296 (1956); *Chem. Abstr.* **53**, 20567 (1959).

²⁴⁹ A. Hoffer, in "International Review of Neurobiology" (C. C. Pfeiffer and J. R. Smythies, eds.), Vol. **4**, p. 307. Academic Press, New York, 1962.

2. "Lutin" Procedure for Adrenaline and Noradrenaline

In the "lutin" procedure (sometimes rather unfortunately called the "trihydroxyindole" procedure, since adrenolutin is usually formulated as 3,5,6-trihydroxy-*N*-methylindole although infrared spectroscopy suggests that in the solid state, at least, adrenolutin should be formulated in the keto form, i.e. as 2,3-dihydro-5,6-dihydroxy-3-oxo-*N*-methylindole¹⁰⁸) many different oxidizing agents have been employed to effect the initial oxidation of the catecholamines,²⁵⁰ but iodine, potassium ferricyanide, and manganese dioxide have been the most extensively used. The oxidation stage is carried out in an aqueous buffer, usually of the phosphate or acetate type. However, there is much confusion in the literature as to the best oxidant to use, the best buffer, the optimum reaction time, the optimum pH for the oxidation of each catecholamine, etc. The fact that adrenaline and noradrenaline are oxidized at different rates at acid pH's has been utilized in the simultaneous determination of each substance in mixtures of the two (see ref. 3 for a survey of early references).

The use of zinc sulfate to catalyze the potassium ferricyanide oxidation procedure²⁵¹ is worthy of comment. It is possible that other metals would also catalyze this oxidation, but their presence in the system would have a deleterious effect on the fluorescence of the final product, while Zn^{++} ions have relatively little effect. For instance, Cu^{++} ions would be expected to catalyze the oxidation stage, but they would also have a strong quenching effect on the fluorescence of the final products.¹⁴⁴ Some of the Zn^{++} ions will also presumably be removed from the solution as insoluble zinc ferrocyanide. Anton and Sayre have recently questioned the value of zinc sulfate as a catalyst at low pH.²⁵²

In the "lutin" procedure the conversion of the non-fluorescent aminochrome into the fluorescent "lutin" is effected by a solution of ascorbic acid in alkali (usually a 9:1 mixture of 20% aqueous sodium hydroxide and 2% aqueous ascorbic acid). The actual protective action of the ascorbic acid under these conditions is not known. No thought appears to have been given by the majority of the workers

²⁵⁰ F. D. Snell and C. T. Snell, "Colorimetric Methods of Analysis," Vol. 3A, p. 111. Van Nostrand, New York, 1961.

²⁵¹ U. S. von Euler and I. Floding, *Acta Physiol. Scand.* **33**, Suppl. 118, 45 (1955).

²⁵² A. H. Anton and D. F. Sayre, *J. Pharmacol. Exp. Therap.* **138**, 360 (1962).

in this field to the fate of the ascorbic acid in the strong alkali. It is of interest to note in this respect that von Euler and Lishajko reported that the alkaline ascorbate mixture is in fact unstable and that this reagent rapidly becomes colored with an accompanying increase in the "blank" fluorescence.²⁵³ In cases where the reaction mixture is acidified prior to determination of the fluorescence,²⁵⁴ the protective action could possibly be due to dehydroascorbic acid (which could be expected to form from ascorbic acid under these conditions) forming a complex with the *o*-dihydroxy group of the 5,6-dihydroxyindoxyl.¹⁶⁰

There are vast differences in the quoted relative fluorescences of the fluorophores obtained from adrenaline and noradrenaline (i.e. adrenolutin and noradrenolutin). With one exception (Anton and Sayre²⁵²), noradrenolutin is reported to be less fluorescent (on a w/w basis) than adrenolutin. This, however, is not true, since experiments with crystalline noradrenolutin^{70, 71} have shown that (i) noradrenolutin is approximately twice as fluorescent as adrenolutin,²⁵⁵ and (ii) it is somewhat more stable than adrenolutin in aqueous solution²⁵⁵ (cf. ref. 256). The use of "internal standards" has, however, allowed the method to function, more or less satisfactorily, in most cases.

A detailed consideration of the chemistry involved in the many modifications of the reaction parameters employed in variations of the "lutin" procedure is outside the scope of this article. References 92 and 257-265, in addition to those mentioned above, will serve as a guide to further reading on the subject.

²⁵³ U. S. von Euler and F. Lishajko, *Acta. Physiol. Scand.* **51**, 348 (1961).

²⁵⁴ H. L. Price and M. L. Price, *J. Lab. Clin. Med.* **50**, 769 (1957).

²⁵⁵ R. A. Heacock and M. E. Mahon, unpublished observations (1963) [cf. *Chem. Can.* **15**, No. 10, 48 (1963)].

²⁵⁶ S. Roston, *Anal. Chem.* **30**, 1363 (1958).

²⁵⁷ J. A. Radley and J. Grant, "Fluorescence Analysis in Ultraviolet Light," 4th ed., p. 327. Chapman and Hall, London, 1954.

²⁵⁸ H. Persky, *Methods Biochem. Anal.* **2**, 57 (1955).

²⁵⁹ U. S. von Euler, "Noradrenaline-Chemistry, Physiology, Pharmacology and Clinical Aspects," p. 85. Charles C. Thomas, Springfield, Ill., 1956.

²⁶⁰ U. S. von Euler, *Pharmacol. Rev.* **11**, 262 (1959).

²⁶¹ T. L. Sourkes and B. D. Drujan, *Can. J. Biochem. Physiol.* **35**, 711 (1957).

²⁶² G. Cohen and M. Goldenberg, *J. Neurochem.* **2**, 58 (1957).

²⁶³ G. Cohen and M. Goldenberg, *J. Neurochem.* **2**, 71 (1957).

²⁶⁴ A. F. DeSchaepe dryver, *Arch. Intern. Pharmacodyn.* **115**, 233 (1958).

²⁶⁵ P. A. Shore and J. S. Olin, *J. Pharmacol. Exp. Therap.* **122**, 295 (1958).

3. Dopamine Assay Procedures

Assay procedures for dopamine which are superficially similar to the "lutin" procedure described above have been reported recently.²⁶⁶⁻²⁶⁸ The chemistry of the production of the fluorophore from dopamine is, however, somewhat different; since the fluorophore is not a 5,6-dihydroxyindoxyl, it is incorrect to refer to the "trihydroxyindole" fluorophore of dopamine (cf. ref. 252). Oxidation of the extracted catecholamine is usually carried out with iodine,²⁶⁶⁻²⁶⁸ presumably with the formation of 7-iodonorepineochrome. The aminochrome is subsequently rearranged to 5,6-dihydroxyindole (it is probable that deiodination accompanies the rearrangement in this case) by a solution of sodium sulfite in aqueous alkali; the solution is acidified before measuring the fluorescence of the product (which is said to form relatively slowly and to be very stable).²⁶⁶⁻²⁶⁸ Irradiation of the reaction mixture with ultraviolet light accelerates the maximal development of fluorescence.²⁶⁶ Since acidification will produce sodium bisulfite in the reaction mixture, it is probable that the fluorophore is a 5,6-dihydroxyindole-sodium bisulfite addition complex. Complexes of this type are known to be both fluorescent and relatively stable in dilute acid solution.^{118, 123, 156, 255} They also form relatively slowly.²⁵⁵

It has been claimed in a recent paper that oxidation with manganese dioxide, followed by rearrangement with alkaline zinc sulfite, gives better results and avoids the necessity of irradiating the products to insure rapid and total development of fluorescence.²⁶⁹

4. The "Ethylenediamine" Procedure

The assay procedure for catecholamines based on the formation of fluorescent products with ethylenediamine, originally described by Weil-Malherbe and Bone,^{197, 198, 270} and considered by some workers to be the most sensitive method, suffers to some extent by a lack of specificity since catechol and 3,4-dihydroxymandelic acid give the same fluorophore as noradrenaline. However, most of the interfering compounds can be eliminated by use of suitable extraction procedures.

²⁶⁶ A. Carlsson and B. Waldeck, *Acta Physiol. Scand.* **44**, 293 (1958).

²⁶⁷ B. D. Drujan, T. L. Sourkes, D. S. Layne, and G. F. Murphy, *Can. J. Biochem. Physiol.* **37**, 1153 (1959).

²⁶⁸ F. Bischoff and A. Torres, *Clin. Chem.* **8**, 370 (1962).

²⁶⁹ V. J. Uuspää, *Ann. Med. Exp. Biol. Fenniae (Helsinki)* **41**, 194 (1963).

²⁷⁰ H. Weil-Malherbe and A. D. Bone, *J. Clin. Pathol.* **10**, 138 (1957).

Although the structures of the fluorophores from adrenaline and noradrenaline are known (see Section IV, H), that (or those) obtained from dopamine has not yet been identified. There is a considerable volume of literature on this method; however, the basic chemistry of this procedure is described in Section IV, H and space does not permit an extensive review of the various experimental methods that have been employed. For further reading, the method is adequately discussed in publications by the following authors: Weil-Malherbe,^{197, 198, 270, 271} Manger,^{272, 273} Valk and Price,²⁷⁴ Nadeau and Joly,²⁷⁵ and Nadeau and Sobolewski.²⁷⁶

5. The Sodium Bisulfite Addition Product Procedure

A sensitive spectrophotometric method based on the strong absorption of the aminochrome-sodium bisulfite addition products (see Section IV, F) at *ca.* 350 m μ has been described recently by van Espen¹²⁸ and Oesterling and Tse^{277, 278} for determining total catecholamines. While not as sensitive as the fluorimetric procedures, this method is considerably more sensitive than the older colorimetric methods based on the visible absorption peak of the aminochromes. Also, it does not have many of the disadvantages (e.g. costly equipment and unstable blanks) often associated with fluorimetric techniques. The basic procedure can be satisfactorily applied to the differential determination of mixtures of adrenaline, noradrenaline, dopamine, metanephrine, and normetanephrine.¹⁷⁸

VI. Some Closely Related Compounds

A. INDOLINE-4,7-QUINONES

Several indoline-4,7-quinones, compounds which might be considered to be *p*-quinonoid aminochromes, have recently been described.^{279, 280} 6-Hydroxyindoline-4,7-quinone (**100**) was obtained

²⁷¹ H. Weil-Malherbe, *Pharmacol. Rev.* **11**, 278 (1959).

²⁷² W. M. Manger, "Chemical Quantitation of Epinephrine and Norepinephrine in Plasma." Charles C. Thomas, Springfield, Ill., 1959.

²⁷³ W. M. Manger, *Pharmacol. Rev.* **11**, 289 (1959).

²⁷⁴ A. T. Valk and H. L. Price, *J. Clin. Invest.* **35**, 837 (1956).

²⁷⁵ G. Nadeau and L-P. Joly, *Can. J. Biochem. Physiol.* **37**, 231 (1959).

²⁷⁶ G. Nadeau and G. Sobolewski, *Can. J. Biochem. Physiol.* **37**, 441 (1959).

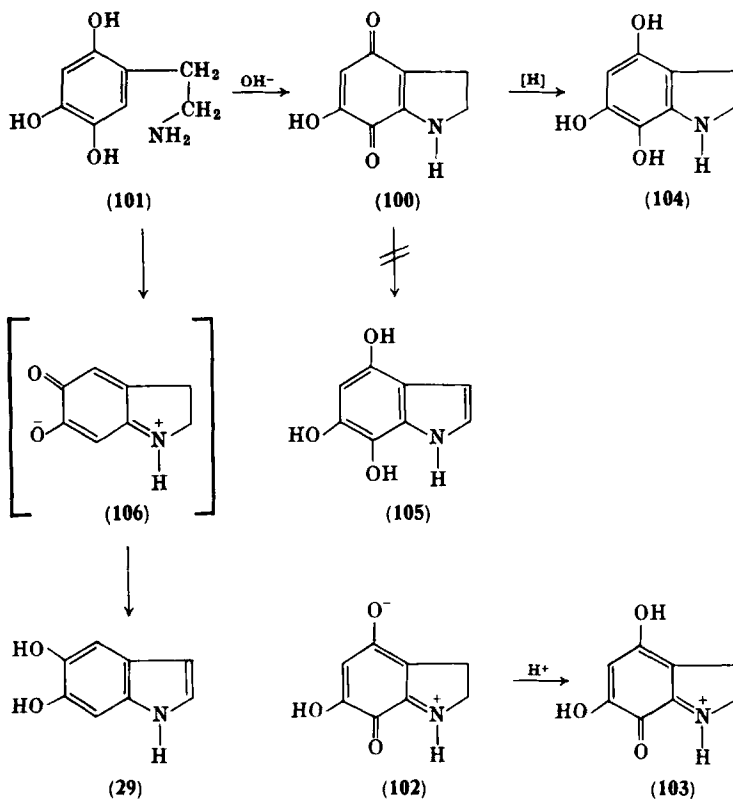
²⁷⁷ R. L. Tse and M. J. Oesterling, *Clin. Chim. Acta* **4**, 307 (1959).

²⁷⁸ M. J. Oesterling and R. L. Tse, *Am. J. Med. Technol.* **27**, 112 (1961).

²⁷⁹ S. Senoh and B. Witkop, *J. Am. Chem. Soc.* **81**, 6231 (1959).

²⁸⁰ J. Daly, L. Horner, and B. Witkop, *J. Am. Chem. Soc.* **83**, 4787 (1961).

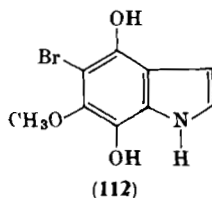
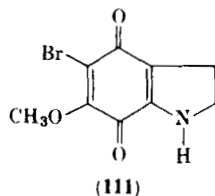
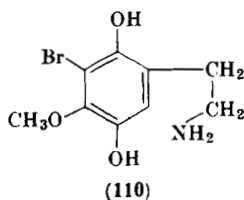
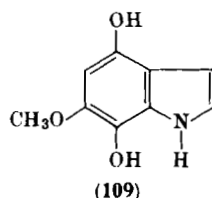
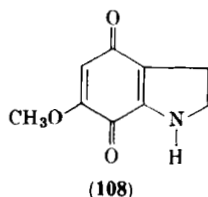
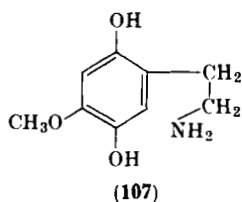
on autoxidation of β -(2,4,5-trihydroxyphenyl)ethylamine (**101**) in weakly alkaline solution.²⁷⁹ The visible absorption maximum of the *p*-quinone **100** shifted from 495 $m\mu$ at mildly alkaline pH to 385 $m\mu$ in acid solution. A similar shift of the visible absorption maximum to shorter wavelengths occurs with the conventional aminochromes in



acid solution (see Section III, B, 1). If, as might be expected by analogy with the *o*-quinonoid aminochromes, compound **100** exists mainly in the zwitterionic form, i.e. as **102**, protonation of such a system would give **103** containing the ortho-quinonoid chromophore (as suggested by Senoh and Witkop) which would be expected to absorb at *ca.* 390 $m\mu$. Reduction of **100** afforded the true leuco compound, 4,6,7-trihydroxyindoline (**104**). The *p*-quinonoid aminochrome **100** does not, however, undergo a base-catalyzed internal

"auto-reduction"-type rearrangement to give 4,6,7-trihydroxyindole (**105**),^{279, 280} as might have been expected by analogy with the behavior of the *o*-quinonoid aminochromes (see Section IV, B, 2).

Harley-Mason has shown that 5,6-dihydroxyindole (**29**) can also be obtained from β -(2,4,5-trihydroxyphenyl)ethylamine (**101**). Oxidation of **101** with potassium ferricyanide, buffered with sodium bicarbonate, gives a deep red solution [presumably containing norepinochrome (**106**)] from which **29** was obtained, after the solution had been allowed to stand under hydrogen for 24 hours.²⁸¹



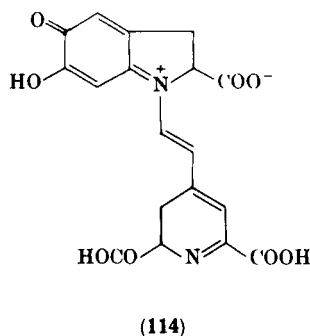
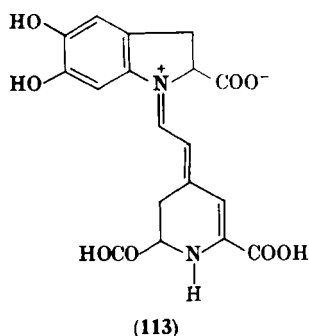
Two other *p*-quinonoid aminochromes are known, namely 6-methoxyindoline-4,7-quinone (**108**) and 5-bromo-6-methoxyindoline-4,7-quinone (**111**),^{279, 280} which were obtained from β -(2,5-dihydroxy-4-methoxyphenyl)ethylamine (**107**) and β -(3-bromo-2,5-dihydroxy-4-methoxyphenyl)ethylamine (**110**), respectively.^{279, 280} (In the earlier publication, **108** and **111** were incorrectly described as indoline-6,7-quinone derivatives.²⁷⁹) The bromo derivative **111** was obtained as a bright red crystalline solid, m.p. 123–126°; cf. ref. 279. In marked contrast to the 6-hydroxyindoline-4,7-quinone (**100**), both the 6-methoxy derivatives **108** and **111** readily undergo the base-catalyzed internal oxidation-reduction reaction to give 4,7-dihydroxy-6-methoxyindole (**109**) and 5-bromo-4,7-dihydroxy-6-methoxyindole (**112**), respectively.^{279, 280} The bromo compound (**111**) could be rearranged to the corresponding 4,7-dihydroxyindole (**112**) by (i) refluxing in *t*-butanol, (ii) sublimation, and (iii) base catalysis.²⁷⁹

²⁸¹ J. Harley-Mason, *J. Chem. Soc.* 200 (1953).

B. MISCELLANEOUS RELATED COMPOUNDS

1. *Betanidin*

The aglycone of betanin, the red-violet pigment of the beet (*Beta vulgaris* var. *rubra*), known as betanidin, has recently been shown to have the structure depicted in structural formula 113.^{170, 282} Betanidin had previously been reported by Piattelli and Minale to contain a dopachrome unit in its structure and consequently would have been formulated as 114.¹⁶⁹ The Italian workers obtained pyrrole-2,3,5-tricarboxylic acid and pyridine-2,4,6-tricarboxylic acid on permanganate oxidation of betanidin and they also prepared a semicarbazone of the pigment, the absorption spectrum of which showed the pH dependency expected for an aminochrome semicarbazone.¹⁶⁹



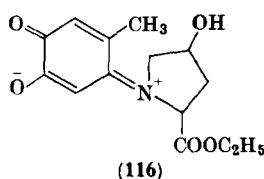
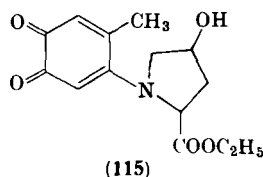
Wyler *et al.*, however, believe that the aminochrome monosemicarbazone obtained by Piattelli and Minale was in fact dopachrome monosemicarbazone, formed after decomposition of the betanidin molecule, which occurs readily in air.^{170, 282}

2. *Some 1-Amino-3,4-benzoquinones*

The red pigment isolated in crystalline form from the reaction products of 1-methyl-3,4-benzoquinone and 4-hydroxyproline ethyl ester was identified as 4-(4'-hydroxy-2'-carbethoxy-1'-pyrrolidyl)-5-methyl-1,2-benzoquinone (115).²⁸³ This highly colored compound should probably be formulated as a zwitterion (116). Similar pigments can be obtained by the interaction of *o*-benzoquinone with proline, hydroxyproline, pyrrolidine, and glycine. Suzuki has shown

²⁸² A. S. Dreiding, *Chimia (Aarau)* **17**, 303 (1963).

²⁸³ H. Jackson and L. P. Kendal, *Biochem. J.* **44**, 477 (1949).

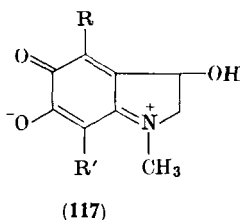


that similar pigments ($\lambda_{\text{max.}}$ ca. 520 $\text{m}\mu$), which are presumably also derivatives of 4-amino-*o*-benzoquinone, are obtained from the polyphenolase-induced oxidation of catechol in the presence of several amino acids.²⁸⁴

The red products obtained from the interaction of tyrosine and either *o*- or *p*-benzoquinone described by Bouchilloux²⁸⁵ are probably 4-amino-*o*-quinone and 3-amino-*p*-quinone derivatives, respectively.

Notes Added in Proof

Three new aminochromes have been described recently, namely 4-methyladrenochrome (117A),²⁸⁶ 7-methyladrenochrome (117B),²⁸⁶ and 7-iodo-4-methyladrenochrome (117C).²⁸⁶ It was impossible to



117A; R = CH₃, R' = H

117B; R = H, R' = CH₃

117C; R = CH₃, R' = I

prepare an iodo derivative of 7-methyladrenochrome,²⁸⁶ confirming that the 7-position is the normal position for iodination of the aminochrome nucleus (cf. ref. 70). The visible absorption maximum of aqueous solutions of 7-methyladrenochrome (117B), which are violet in color, occurs at a considerably longer wavelength (i.e. 534 $\text{m}\mu$) than is usual for non-halogenated aminochromes. Although no spectral data have been reported previously for 7-methylsubstituted aminochromes, 7-methyldopachrome and 4,7-dimethylnorepinochrome have been prepared in solution, and these solutions were described as being deep violet in color.²⁸⁷

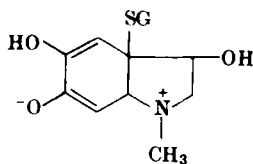
²⁸⁴ Y. Suzuki, *Enzymologia* **19**, 289 (1958).

²⁸⁵ S. Bouchilloux, *Bull. Soc. Chim. Biol.* **43**, 1299 (1961).

²⁸⁶ R. A. Heacock and O. Hutzinger, *Can. J. Chem.* in press (1965).

²⁸⁷ R. I. T. Cromartie and J. Harley-Mason, *J. Chem. Soc.* 3525 (1953).

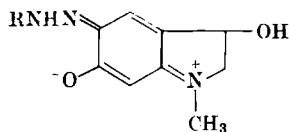
The main products obtained from the reaction between adrenochrome (1) and glutathione have been shown to result from the 1,4-addition of glutathione to the C-5 unsaturated carbonyl systems in 1 involving the C₆-C₇ and the C₄-C₉ double bonds and are probably *S*-[7-(5,6-dihydroxy-*N*-methylindolyl)]glutathione (65B) and 9-*S*-glutathionyl-2,3,6,9-tetrahydro-3,5-dihydroxy-6-oxo-*N*-methylindole (118), respectively.^{288, 289} It was confirmed that 5,6-dihydroxy-*N*-methylindole (28) is also a product of this reaction.^{288, 289} A more



(118)

detailed study of the reaction between 7-iodoadrenochrome (12) and glutathione has recently confirmed that a mixture of products results, including 5,6-dihydroxy-7-iodo-*N*-methylindole (55), *S*-[7-(5,6-dihydroxy-*N*-methylindolyl)]glutathione (65B), *S*-[4-(5,6-dihydroxy-7-iodo-*N*-methylindolyl)]glutathione (66), and traces of 5,6-dihydroxy-*N*-methylindole (28).²⁹⁰

In recent months a relatively large number of new aminochrome hydrazone derivatives have been reported. Yamanishi *et al.* have reported the synthesis of twenty-one adrenochrome hydrazone derivatives (cf. 119) where R = oxalyl, oxamyl, malonyl, succinyl,



(119)

guanyl, guanyl (methanesulfonate), guanyl (sulfate), benzoyl, salicyl, *p*-hydroxybenzoyl, *o*-aminobenzoyl, *p*-nitrobenzoyl, *p*-chlorobenzoyl, *o*-carboxyphenyl, *p*-thiocyanophenyl, *p*-sulfophenyl, *p*-tolyl, di-

²⁸⁸ R. A. Heacock and G. L. Mattok, *Arch. Biochem. Biophys.* **107**, 352 (1964).

²⁸⁹ G. L. Mattok and R. A. Heacock, *Can. J. Chem.* **43**, 119 (1965).

²⁹⁰ G. L. Mattok and R. A. Heacock, unpublished work (1964).

phenyl, α -methylphenyl, naphthyl, and cinnamoyl.²¹⁹ These authors reported the solubility of these compounds in water, sesame seed oil, propylene glycol, and 5% sodium salicylate solution.²⁹¹ The methane-sulfonate and sulfate of the guanyl derivatives, i.e. **119** [$R = NH_2C(=NH)NH-$], are very soluble in water, being about 600 and 50 times more soluble in water, respectively, than adrenochrome monosemicarbazone.²⁹¹ The relative stabilities of these aminochrome hydrazone derivatives in aqueous solutions at pH 2 and at pH 12 were also reported.²⁹¹ The preparation of **119** [$R = NH_2C(=NH)NH-$] and a number of its water-soluble salts has also been recently described in the patent literature.^{292, 293}

A number of other aminochrome monosemicarbazones have been described recently including: adrenochrome β -hydroxyethyl ether monosemicarbazone.²⁹⁴ 4-methyladrenochrome monosemicarbazone,²⁸⁶ and 7-methyladrenochrome monosemicarbazone.²⁸⁶ The preparation of a number of 7-halogenated aminochrome monoximes, monosemicarbazones, and monohydrazones (prepared by direct halogenation of the parent aminochrome derivative), which are reported to be potent hypotensive agents, has also recently been reported.²⁹⁵ A further report of the preparation of a number of derivatives of the adrenochrome—*O*-aminoglycollic acid condensation product has appeared²⁹⁶ (cf. ref. 185). A 1 : 1 molecular compound of adrenochrome monosemicarbazone and adenine (m.p. 273°) has also been described.²⁹⁷ A number of reports dealing with the efficiency of various additives in increasing the water-solubility of adrenochrome monosemicarbazone²⁹⁸⁻³⁰¹ and of *N*-isopropylnoradrenochrome monoisonicotinylhydrazone³⁰² have appeared in the past few months.

²⁹¹ Y. Yamanishi, S. Kikumoto, M. Kakemi, and M. Yokogawa, *Yakuzaiigaku* **23**, 128 (1963); *Chem. Abstr.* **60**, 1678 (1964).

²⁹² Shiraimatsu New Drug Co., Japanese Patent 17,034 (1963); *Chem. Abstr.* **60**, 2898 (1964).

²⁹³ Shiraimatsu New Drug Co., Fr. M2689 (1964); *Chem. Abstr.* **62**, 529 (1965).

²⁹⁴ J. Hukki and N. Seppäläinen, Finnish Patent 33,069 (1963); *Chem. Abstr.* **61**, 8280 (1964).

²⁹⁵ N. Barsel, U.S. Patent. 3,098,858 (1963); *Chem. Abstr.* **60**, 506 (1964).

²⁹⁶ J. H. Murtori, Spanish Patent 286,974 (1963); *Chem. Abstr.* **61**, 1835 (1964).

²⁹⁷ Shiraimatsu New Drug Co., Japanese Patent 14,939 (1963); *Chem. Abstr.* **60**, 4161 (1964).

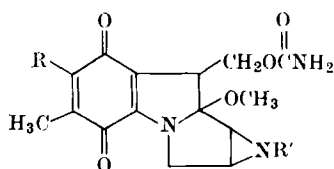
²⁹⁸ Sanawa Chemical Research Laboratories, Japanese Patent 13,489 (1962); *Chem. Abstr.* **60**, 5288 (1964).

²⁹⁹ Sanawa Chemical Research Laboratories, Japanese Patent 13,490 (1962); *Chem. Abstr.* **60**, 5288 (1964).

The removal of the semicarbazide residue from aminochrome mono-semicarbazones by alkaline degradation has been reported.³⁰³ The resulting 6-hydroxyindole derivatives could be readily isolated as their methyl ethers.³⁰³

A procedure for the fluorimetric determination of 3-methoxytyramine was described by Carlsson and Waldeck in 1964.³⁰⁴ This procedure, which resembled the dopamine assay procedures previously described (cf. Section V, E, 3), involved the oxidation of the amine with iodine, presumably to an aminochrome (cf. the oxidation of metanephrine (Section II, D, 1)) which was subsequently rearranged to a fluorescent derivative.³⁰⁴

The mitomycins (cf. refs. 305–307), an important group of antibiotics, could be considered to be *p*-quinonoid aminochromes (cf. Section VI, A), e.g. mitomycin A (**120A**) (λ_{\max} 218, 320, and 520 m μ) and porfiromycin (**120B**) (λ_{\max} 217, 360, and 555 m μ).



(120)

120A; R = CH₃O, R' = H

120B; R = NH₂, R' = CH₃

³⁰⁰ Chugai Pharmaceutical Co., Japanese Patent 4,893 (1963); *Chem. Abstr.* **59**, 3724 (1963).

³⁰¹ S. Goto and S. Iguchi, *Yakugaku Zasshi* **83**, 435 (1963); *Chem. Abstr.* **59**, 13926 (1963).

³⁰² N. Barsel, J. Goodman, H. Ross, and R. Forman, British Patent 911,727 (1962); *Chem. Abstr.* **58**, 10180 (1963).

³⁰³ R. A. Heacock and O. Hutzinger, *J. Chem. Soc.* in press (1965).

³⁰⁴ A. Carlsson and B. Waldeck, *Scand. J. Clin. Lab. Invest.* **16**, 133 (1964).

³⁰⁵ J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer, R. P. Williams, C. F. Wolf, W. Fulmor, C. Pidaacks, and J. E. Lancaster, *J. Am. Chem. Soc.* **84**, 3185 (1962).

³⁰⁶ E. R. Garrett, *J. Med. Chem.* **6**, 488 (1963).

³⁰⁷ C. L. Stevens, K. G. Taylor, M. E. Munk, W. S. Marshall, K. Noll, G. D. Shah, L. G. Shah, and K. Uzu, *J. Med. Chem.* **8**, 1 (1965).

Aromatic Quinolizines

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I. Introduction

Since the last extensive review¹ on the chemistry of the quinolizines was presented, numerous developments have occurred in the field of natural products incorporating the quinolizine nucleus as well as in the synthesis and study of the simple quinolizine derivatives. The present chapter is confined exclusively to the contributions made in the field of the aromatic quinolizine derivatives.

The quinolizinium ion, the parent compound of the aromatic quinolizines, is a cationic aromatic system like the pyrylium or thia-pyrylium cation. It is isoelectronic with naphthalene. The parent

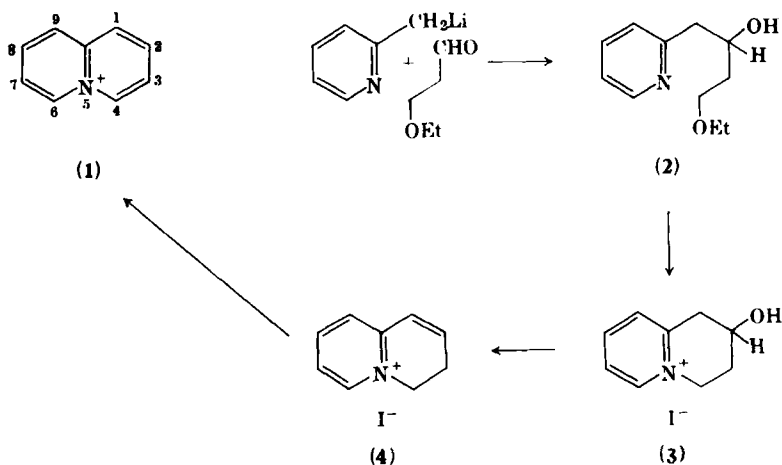
¹ B. S. Thyagarajan, *Chem. Rev.* **54**, 1019 (1954).

compound and the numbering of the ring system are shown in formula 1.

II. Syntheses of Quinolizine Derivatives

A. ALKYL, ARYL, AND HETERO-RING SUBSTITUTED QUINOLIZINES AND BENZOLOGS

One of the significant developments in the chemistry of the quinolizines since 1954 was the synthesis of the parent aromatic system, the quinolizinium ion, which was unknown until then. This was achieved by Boekelheide and Gall² by the condensation of 2-picolyllithium with β -ethoxypropionaldehyde followed by the steps indicated in the sequence $2 \rightarrow 3 \rightarrow 4 \rightarrow 1$.



This sequence of reactions was later repeated³ with 2,6-lutidyllithium to give the corresponding 6-methylquinolizinium ion in improved yield. Several related syntheses based on this pattern were reported by other groups of workers^{4, 5, 6} soon after. Richards and Stevens⁴ reported the formation of 2-ethyl-3-methylquinolizinium

² V. Boekelheide and W. G. Gall, *J. Am. Chem. Soc.* **76**, 1832 (1954).

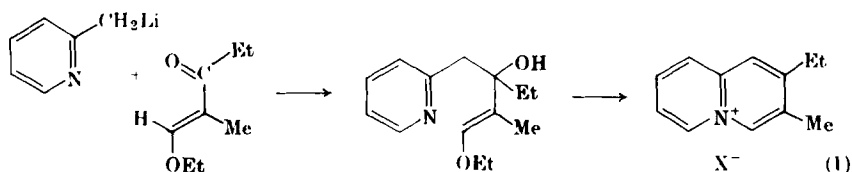
³ V. Boekelheide and J. M. Ross, *J. Am. Chem. Soc.* **77**, 5691 (1955).

⁴ A. Richards and T. S. Stevens, *Chem. Ind. (London)* 905 (1954).

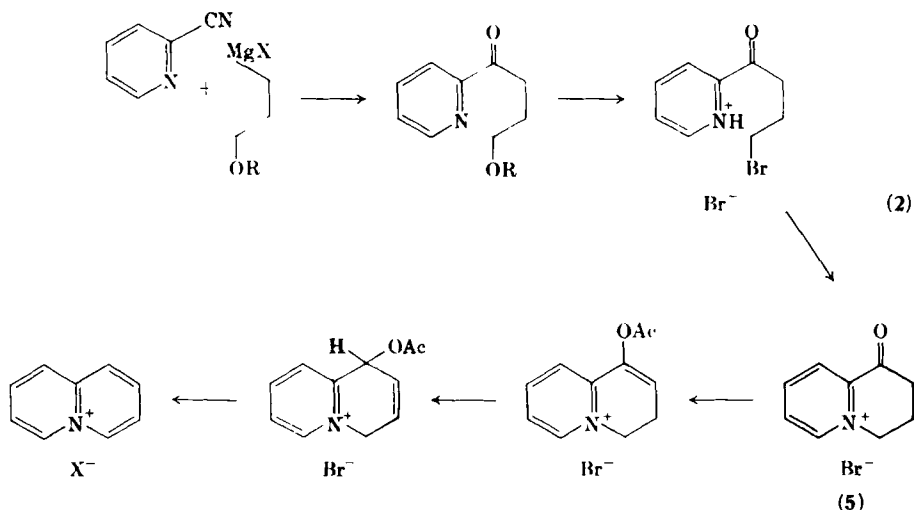
⁵ K. W. Wischmann, A. V. Logan, and D. M. Stuart, *J. Org. Chem.* **26**, 2794 (1961).

⁶ A. Richards and T. S. Stevens, *J. Chem. Soc.* 3067 (1958).

derivatives by the condensation of picolylithium with ethoxymethylene diethyl ketone as illustrated in Eq. (1).



Aromatization of a tetrahydroquinolizone (5) by means of acetic anhydride and sulfuric acid or acetic anhydride alone leads to the formation of a variety of mono- or di-substituted quinolinizinium compounds. Glover and Jones^{7, 8} achieved the synthesis of a number of these derivatives starting from 2-cyanopyridine and condensing it with appropriate Grignard reagents followed by cyclization and aromatization as outlined in Eq. (2). An identical method was simultaneously worked out by Nesmeyanov and Rybinskaya⁹ for the specific synthesis of 2-substituted quinolinizinium compounds. This



⁷ E. E. Glover and G. Jones, *Chem. Ind. (London)* 1456 (1956).

⁸ E. E. Glover and G. Jones, *J. Chem. Soc.* 3021 (1958).

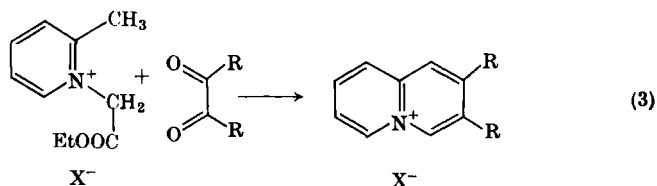
⁹ A. N. Nesmeyanov and M. I. Rybinskaya, *Dokl. Akad. Nauk SSSR* **116**, 93 (1957).

aromatization procedure¹⁰ provides considerable flexibility in the synthesis and leads to substitution at any desired point in the quinolizinium ring, as illustrated by the different derivatives listed in Table I.

TABLE I
QUINOLIZINE DERIVATIVES PREPARED BY AROMATIZATION OF
1,2,3,4-TETRAHYDROQUINOLIZINES

Compound	M.p., °C	Yield, %
Quinolizinium bromide	260-1	96
2-Methylquinolizinium picrate	162	65
3-Methylquinolizinium bromide	189	quant.
4-Methylquinolizinium picrate	135	65
2-Phenylquinolizinium picrate	168	88.4
Benzo[<i>a</i>]quinolizinium picrate	178	66.4
Benzo[<i>b</i>]quinolizinium picrate	215	62
Benzo[<i>c</i>]quinolizinium picrate	188-9	63

Another elegant approach to alkyl- and aryl-substituted quinolizines involves the condensation of α -picolinium salts carrying an active methylene group on the nitrogen atom with suitable α -diketones. Westphal *et al.*¹¹ have reacted 1,2-diketones, e.g. diacetyl, benzil, furil, and pyridil, with 2-methyl-*N*-carbethoxymethylpyridinium halides in the presence of weak bases such as dibutylamine or sodium bicarbonate and obtained the corresponding 2,3-disubstituted quinolizinium halides [Eq. (3)]. Spontaneous hydrolysis and decarboxylation



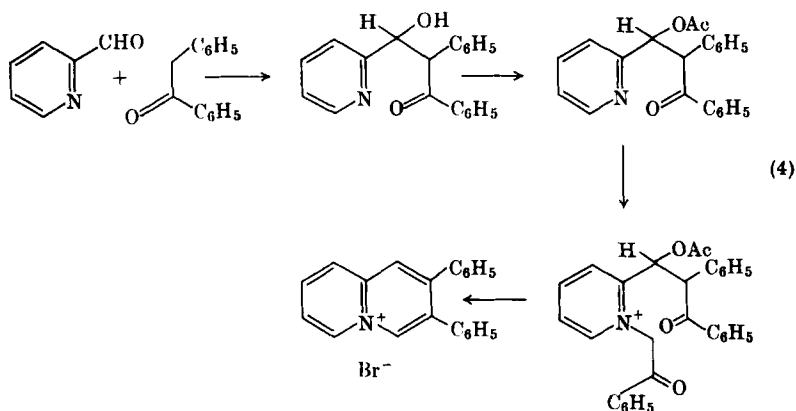
of the carbethoxy group occur and lead directly to the quinolizinium derivative. The yields in this synthesis are good and may be as high as 80%. The necessity for using weak bases for condensation arises from the fact that in strongly alkaline media there is a tendency to form the corresponding indolizines. For instance, *N*-phenacyl-2-picolinium

¹⁰ E. E. Glover and G. Jones, *J. Chem. Soc.* 1686 (1959).

¹¹ O. Westphal, K. Jann, and W. Heffe, *Arch. Pharm.* **294**, 37 (1961).

bromide affords 2-phenylindolizine¹² under strongly alkaline conditions. In the case of the *N*-carbethoxymethyl-2-picolinium derivative this situation does not prevail. But even in the *N*-phenacyl compound, the formation of the indolizine derivative can be minimized by the addition of increased amounts of the reacting α -diketones. The synthesis can easily be extended to a number of other derivatives by starting from 2-ethylpyridinium or 2,6-lutidinium salts. This elegant synthesis has, however, one drawback. If the *N*-methylene group is made more reactive, the reactivity of the α -methyl group towards condensation diminishes because of the tendency to form the corresponding methylene bases.

Some variations on the above scheme have also been successfully adapted to the synthesis of other related quinolizines. One of these involves the condensation of pyridine-2-aldehyde with deoxybenzoin¹³ followed by quaternization with phenacyl halides and cyclization by treatment with dibutylamine [Eq. (4)].

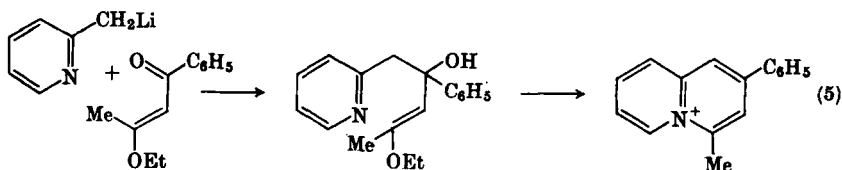


The principle of condensation with diketones has further been extended by using 1,3-diketones to form 2,4-disubstituted quinolizines.¹⁴ In general the reaction involves the condensation of 2-picolyl lithium with the enol ether or the monoketal of a β -dicarbonyl compound followed by cyclodehydration of the resulting carbinol by means of acid. This scheme is illustrated in Eq. (5).

¹² A. E. Tschitschibabin, *Ber.* **60**, 1607 (1927).

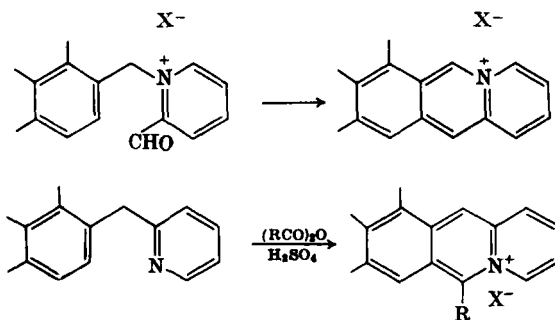
¹³ O. Westphal and G. Feix, *Angew. Chem.* **75**, 206 (1963).

¹⁴ H. V. Hansen and E. D. Amstutz, *J. Org. Chem.* **28**, 393 (1963).



The yields are high in this synthesis. However, the use of strong acids like sulfuric acid in the cyclization step causes much tar formation and lower yields. Acetylacetone, benzoylacetone, and acetoacetaldehyde have been successfully employed as starting β -diketones and afford the corresponding 2,4-disubstituted quinolizines in 50–75% yield. The use of 2,6-lutidyllithium as starting component gave the corresponding 2,4,6-trisubstituted quinolizines.

The Bradsher and Jones method^{15, 16} of cyclizing *N*-acyl-2-benzyl- or -2-phenyl-pyridines, employing hydrobromic acid as condensing agent, constitutes an elegant synthesis for the benzologs of quinolizines. There are two variants to this scheme. One of these starts from either 2-picolinaldehyde or the aldoxime,^{17a} followed by quaternization with benzyl halides and subsequent cyclization to the acridizinium ion^{17b} [Eq. (6)]; it has been observed that the oximes quaternize more readily than the free acyl derivatives. The other method [Eq. (7)] involves cyclization of a 2-arylmethylpyridine with sulfoacetic acid to give the acridizinium ion and is based on the synthesis of coralyn from papaverine.



¹⁵ C. K. Bradsher and J. H. Jones, *J. Am. Chem. Soc.* **79**, 6033 (1957).

¹⁶ C. K. Bradsher and J. H. Jones, *J. Org. Chem.* **25**, 293 (1960).

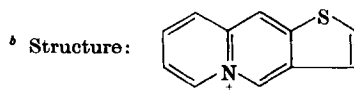
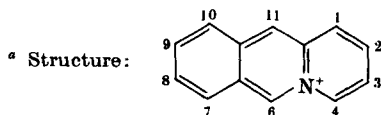
^{17a} C. K. Bradsher, T. W. Solomons, and F. R. Vaughan, *J. Org. Chem.* **25**, 757 (1960).

^{17b} According to the subject index of *Chemical Abstracts* and *The Ring Index*, benzo[b]quinolizinium is the preferred name for this ion.

The compounds synthesized by this method are listed in Table II.

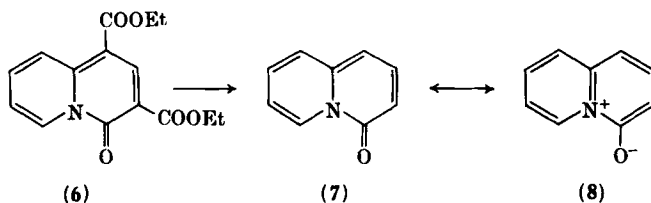
TABLE II
QUINOLIZINIUM DERIVATIVES SYNTHESIZED BY THE METHOD OF
BRADSHER AND JONES

Salt	Yield, %	Reference
9-Methylacridizinium ^a	92.5	17
11-Methylacridizinium	21	17
9,11-Dimethylacridizinium	40	17
8-Hydroxy-11-methylacridizinium	99	17
7,8-Dimethoxyacridizinium	75	15
8,9-Methylenedioxyacridizinium	31	15
7,8-Methylenedioxyacridizinium	42	15
Thieno[2,3- <i>b</i>]quinolizinium ^b	72	33



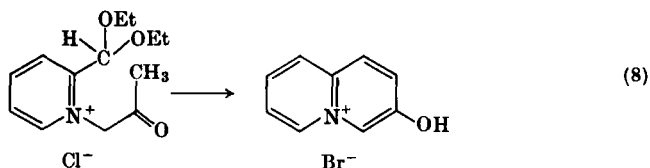
B. HYDROXYQUINOLIZINES

Hydroxyquinolizines have been reported only recently. In this connection the salts of 4-quinolizone may be considered as 4-hydroxy-quinolizinium derivatives. Boekelheide and Lodge¹⁸ hydrolyzed and decarboxylated 1,3-dicarbethoxy-4-quinolizone (6) to the free quinolizone (7) and found that the compound had the characteristics of the quinolizinium cation 8 as indicated by the identity of the ultraviolet spectra determined in neutral and acidic media.

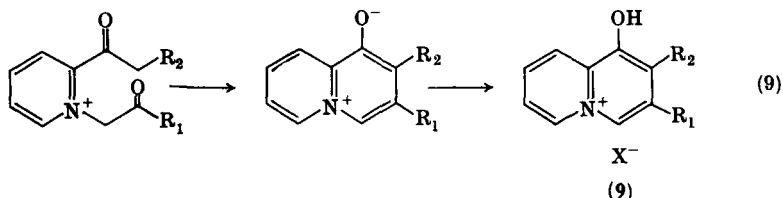


¹⁸ V. Boekelheide and J. P. Lodge, Jr., *J. Am. Chem. Soc.* **73**, 3681 (1951).

3-Hydroxyquinolizinium derivatives were synthesized for the first time in 1962 according to Eq. (8).¹⁹



A direct synthesis of 1-hydroxyquinolizinium salts has been reported only recently.²⁰ This involves the base-catalyzed cyclization of quaternary salts derived from α -bromoketones (e.g. phenacyl bromide) and 2-acylpyridines to give **9** in good yield [Eq. 9].

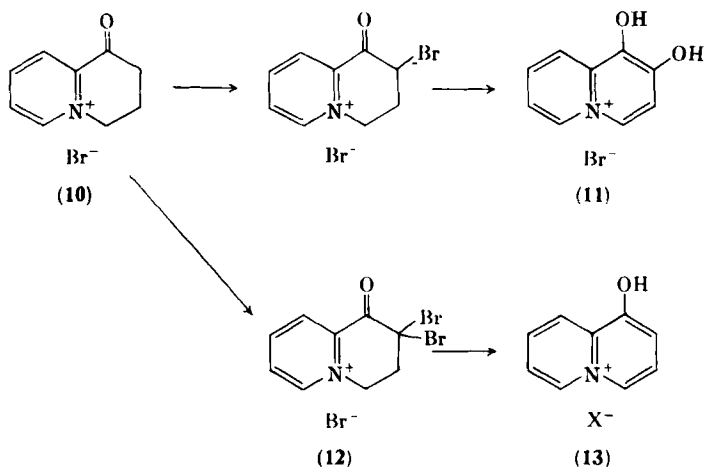


Fozard and Jones²¹ described an independent synthesis of 1-hydroxy- and 1,2-dihydroxy-quinolizinium derivatives. Dehydrogenation of 1,2,3,4-tetrahydro-1-oxoquinolizinium salts led to 1-hydroxyquinolizinium derivatives. Alternatively, diazotization of 1-aminoquinolizinium bromide followed by decomposition of the diazonium salt in the usual manner led to the same 1-hydroxy derivative. However, both of these methods gave the 1-hydroxy compound in very low yield. A better method was to brominate the ketone (**10**) at the 2-position and then treat the bromo derivative with either a strongly basic ion-exchange resin or hot aqueous silver acetate, which led directly to the 1,2-dihydroxyquinolizinium salt (**11**). Bromination of **10** also afforded a 2,2-dibromo compound (**12**) which upon treatment with hot dimethylaniline gave the 1-hydroxyquinolizinium salt (**13**).

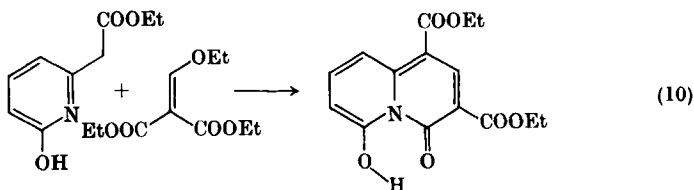
¹⁹ E. Schrauffstatter, *Angew. Chem., Intern. Ed. Engl.* **1**, 593 (1962).

²⁰ W. Weiss, Ph.D. Thesis, University of Giessen, 1963, as quoted by F. Krohnke [*Angew. Chem. Intern. Ed. Engl.* **2**, 225 (1963)].

²¹ A. Fozard and G. Jones, *J. Chem. Soc.* 2203 (1963).



Adams and Reifschneider²² synthesized 6-hydroxy-4-quinolizone according to Eq. (10).



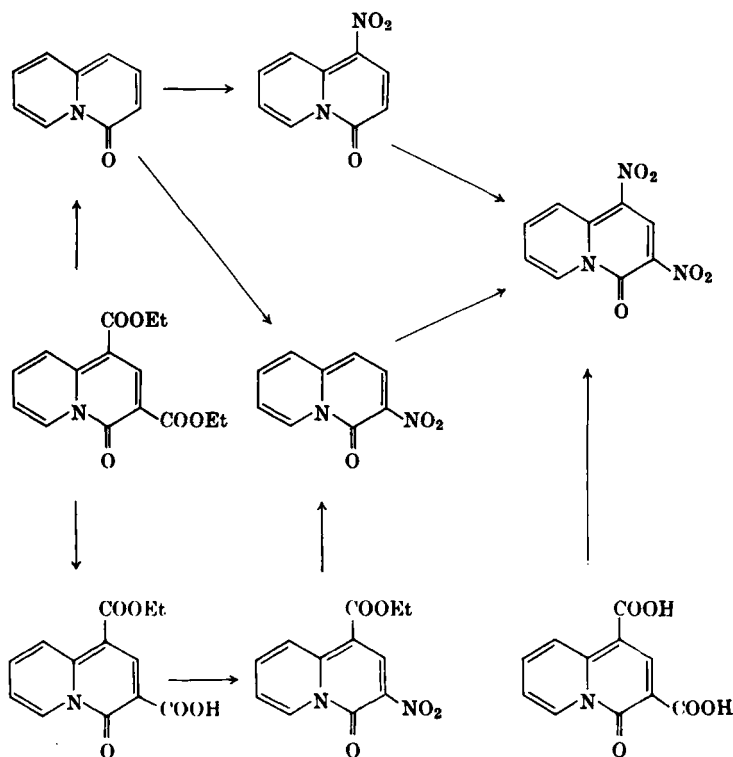
C. NITROQUINOLIZINES

Although no simple nitroquinolizines have been described, the nitration of quinolizones and hydroxyquinolizinium ions has been studied. Fozard and Jones²¹ have reported that nitration of 1-hydroxyquinolizinium salts occurs readily with concomitant formation of complex products. Thyagarajan and Gopalakrishnan²³ have studied the nitration of 4-quinolizone, under different conditions, as outlined in Scheme I. One of the interesting observations in this investigation was the facile displacement of carboxyl groups from the

²² R. Adams and W. Reifschneider, *J. Am. Chem. Soc.* **81**, 2537 (1959).

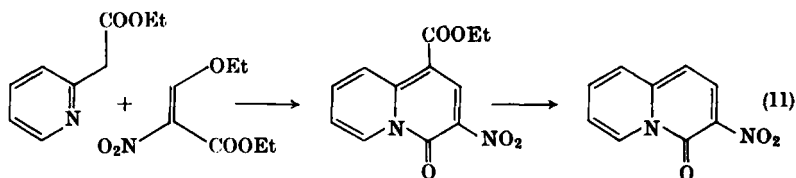
²³ B. S. Thyagarajan and P. V. Gopalakrishnan, *Tetrahedron*, **20**, 1051 (1964).

1- and 3-positions of the 4-quinolizone molecule by the nitro groups. This provided an alternate route to the nitroquinolizones. Direct nitration of 4-quinolizones apparently occurs only on the oxygenated ring since no derivatives were obtained with nitro groups in the non-oxygenated ring.



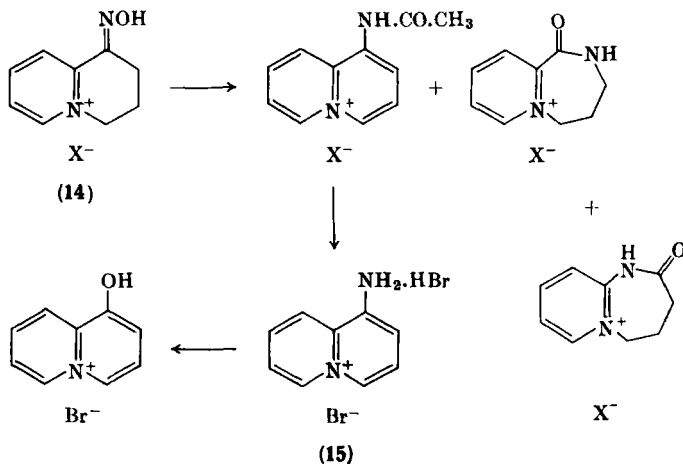
SCHEME I

The nitro derivatives were also obtained by direct synthesis starting from ethyl β -ethoxy- α -nitroacrylate [Eq. (11)].



D. AMINOQUINOLIZINES

Collicutt and Jones²⁴ have recently described the preparation of 1-aminoquinolizinium salts. Beckmann rearrangement of the oxime (14) of 1,2,3,4-tetrahydro-1-oxoquinolizinium bromide gave the 1-acetamido derivative, which on hydrolysis with concentrated hydrobromic acid afforded 1-aminoquinolizinium bromide hydrobromide (15).



Fozard and Jones²¹ have reported the formation of 3-amino-1-hydroxyquinolizinium bromide (probable structure) by the treatment with ammonia of 2,2-dibromo-1,2,3,4-tetrahydro-1-oxo-quinolizinium bromide. A pyridyne-type intermediate is postulated to explain the formation of this compound.

Reduction of nitroquinolizones also leads to aminoquinolizones. On treatment with zinc and hydrochloric acid, 1-carbethoxy-3-nitro-4-quinolizone is converted in reasonable yield into the corresponding 3-amino derivative.²³

E. HALOQUINOLIZINES

The haloquinolizines thus far reported have been prepared mainly by bromination of hydroxyquinolizinium salts or by dehydrobromination of bromo derivatives of 1,2,3,4-tetrahydro-1-oxoquinolizinium

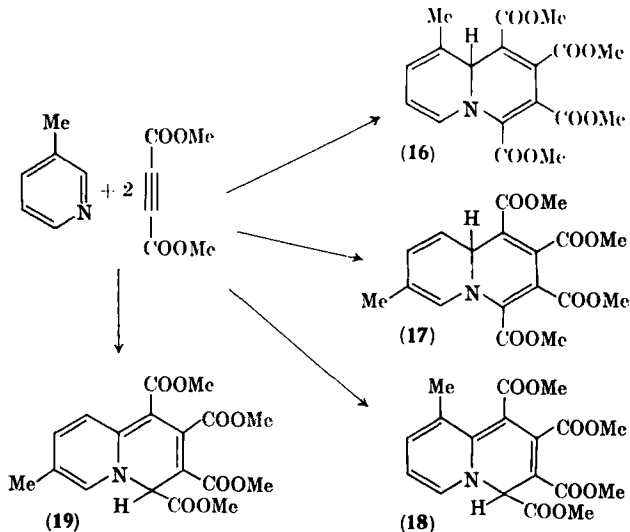
²⁴ A. R. Collicutt and G. Jones, *J. Chem. Soc.* 4101 (1960).

compounds. Heating 2,2-dibromo-1-oxo-1,2,3,4-tetrahydroquinolizinium bromide in concentrated hydrobromic acid or in the dry state gave 1-hydroxy-2-bromoquinolizinium bromide. Bromination of 1-acetoxyquinolizinium bromide readily afforded the 2-bromo-derivative.²¹ However, 1,2-dihydroxyquinolizinium bromide is not brominated by bromine in HBr solution. 3-Bromo-1-hydroxyquinolizinium bromide has been prepared from 3-amino-1-hydroxyquinolizinium bromide by the Sandmeyer reaction.

F. CARBOXYQUINOLIZINES

Following the original pattern of synthesis worked out by Diels and Pistor²⁵ and with a view to verifying the structures of some of the oxidation and hydrolysis products, Acheson and Taylor²⁶ have recently synthesized 9-methyl- and 7,9-dimethyl-4*H*-quinolizine-1,2,3,4-tetracarboxylic esters. On the bases of extensive oxidation and reduction studies and ultraviolet and N.M.R. spectral data, the different labile and stable adducts have been assigned the 9*aH*- (16, 17) or the 4*H*-quinolizine structures (18, 19).

Almost all the carboxy- and carbalkoxy-quinolizones known thus



²⁵ O. Diels and H. Pistor, *Ann. Chem.* **530**, 87 (1937).

²⁶ R. M. Acheson and G. A. Taylor, *J. Chem. Soc.* 1691 (1960).

far carry the acid and ester groups on the pyridone ring. These have been prepared directly by condensing ethyl 2-pyridylacetate with different β -alkoxy- α -substituted-acrylic esters. One of the earliest examples was provided by Boekelheide and Lodge.¹⁸ The reactivity of the different acrylic esters with 2-pyridylacetic esters, nitriles, ketones, and amides varies considerably; some react at room temperature, some require long reaction times, and some stronger heating. The reaction conditions are illustrated in Table III.

TABLE III
PREPARATION OF CARBOXY- AND CARBALKOXY-QUINOLIZONES

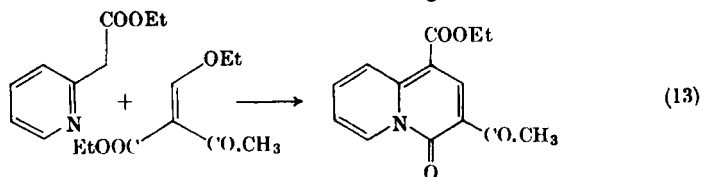
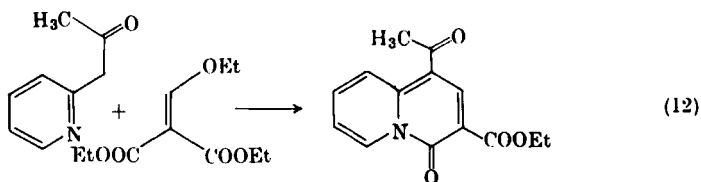
Reactants	Conditions	Yield, %	Refer- ence
Ethyl 2-pyridylacetate + diethyl ethoxymethylenemalonate	8 hr at 180° with removal of alcohol formed concurrently	52	18
Ethyl 2-pyridylacetate + diethyl ethoxymethylenemalonate	NaOEt in EtOH, 0°	67	32
Ethyl 2-pyridylacetate + diethyl ethoxymethylenemalonate	6 hr at 160° without removal of alcohol formed	59-63	27
Ethyl 2-pyridylacetate + ethyl ethoxymethylenenitroacetate	10 min at 60°, 20 min at 100° without removal of alcohol formed	48	27
Ethyl 2-pyridylacetate + ethyl ethoxymethylenecyanoacetate	NaOEt in EtOH, 15 hr at 25°	41	26a
Ethyl 2-pyridylacetate + ethyl ethoxymethyleneacetoacetate	NaOEt (catalytic amount) in benzene, 15 hr at 30°	70	27
2-Pyridylacetone + diethyl ethoxymethylenemalonate	6 hr at 150-160° without removal of alcohol formed	40	27
2-Picoline + diethyl ethoxymethylenemalonate	NaNH ₂ in liquid ammonia	—	26b
2-Pyridylacetone + diethyl ethoxymethylenemalonate	NaOEt in EtOH, 0°	—	32
2-Pyridylacetamide + diethyl ethoxymethylenemalonate	NaOEt in EtOH, 0°	—	32
Ethyl 2-pyridylacetate + ethyl ethoxymethylenecyanoacetate	Na in anhydrous Et ₂ O, stirred 7 hr at 25°	20	26a
Methyl 5-cyano-2-methylnicotinate + diethyl ethoxymethylenemalonate	KOEt in EtOH, refluxed 4 hr, kept 15 hr at 25°	36	26a

^{26a} T. R. Govindachari, S. Rajadurai, M. Subramanyan, and B. S. Thyagarajan, *J. Chem. Soc.* 3839 (1957).

^{26b} F. Bohlmann, A. Englisch, J. Politt, H. Sander, and W. Weise, *Chem. Ber.* 88, 1831 (1955).

G. ACYLQUINOLIZINES

2-Pyridylacetone and diethyl ethoxymethylenemalonate react to give 1-acetyl-3-carbethoxy-4-quinolizone [Eq. (12)], which on hydrolysis and decarboxylation yields 1-acetyl-4-quinolizone.²⁷ 3-Acetyl-1-carbethoxy-4-quinolizone has been similarly converted into 3-acetyl-4-quinolizone²⁷; the latter compound is identical with that synthesized^{27a} from 2-pyridylacetylene. Condensation of ethyl 2-pyridylacetate or 2-pyridylacetone with ethyl ethoxymethyleneacetoacetate affords 3-acetyl-1-carbethoxy- [Eq. (13)] or 1,3-diacetyl-4-quinolizone, respectively.²⁷ The synthesis of 3-benzoyl-4-quinolizone has been reported.^{27a}



III. Reactions of Quinolizines

A. DISPLACEMENT REACTIONS

The pyridyne-type intermediate postulated in the displacement of bromine from 2,2-dibromo-1-oxo-1,2,3,4-tetrahydroquinolizinium bromide is referred to in Section II, D.

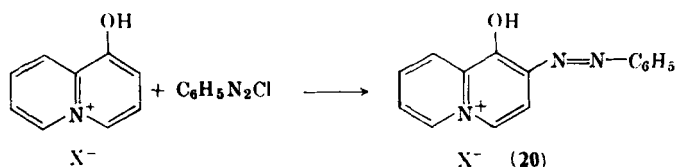
The facile displacement of carboxyl groups from the 1- and 3-positions of 4-quinolizone is mentioned in Section II, C and provides an easy route to the nitroquinolizones. (See *Note Added in Proof*, p. 314.)

B. COUPLING REACTIONS

Diazonium coupling to 1-hydroxyquinolizinium bromide²¹ yields a highly insoluble red product which has been assigned structure **20**. The diazonium salt from 1-hydroxy-3-aminoquinolizinium bromide has been coupled with alkaline β -naphthol.²¹

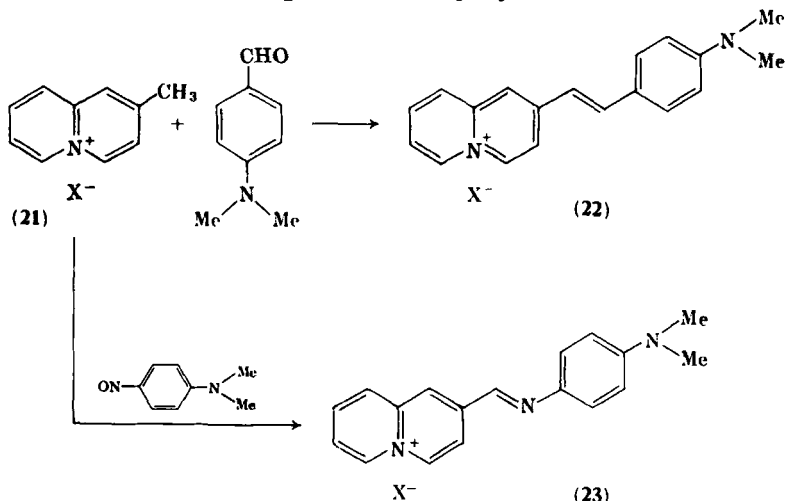
²⁷ B. S. Thyagarajan and P. V. Gopalakrishnan, *Tetrahedron* **21**, 945 (1965).

^{27a} D. Leaver, W. K. Gibson, and J. D. R. Vass, *J. Chem. Soc.* 6053 (1963).



C. CONDENSATIONS OF ACTIVE METHYLENE GROUPS

2-Methylquinolinizinium iodide (21, X = I) has been condensed with *p*-dimethylaminobenzaldehyde to yield the corresponding styryl derivative (22). Reaction of the same compound with *p*-nitrosodimethylaniline affords the Schiff base 23.⁶ The simple 2-styrylquinolinizinium bromide was reported recently by Hansen and Amstutz.¹⁴



These workers also condensed 4-methyl-2-phenylquinolinizinium bromide with *p*-dimethylaminobenzaldehyde, using piperidine as catalyst, and obtained the corresponding styryl derivative in good yield. However, when a methyl group was present in the 6-position, condensation did not occur on the 4-methyl group; for example, 4,6-dimethyl-2-phenylquinolinizinium bromide failed to undergo this condensation. Similarly, 2,4,6-trimethylquinolinizinium bromide also fails to react with benzaldehyde, formaldehyde, *p*-nitro- or *p*-methoxybenzaldehyde. This failure to undergo condensation has been attributed to steric hindrance from the 6-methyl group.¹⁴ Clemo *et al.*²⁸ have

²⁸ G. R. Clemo, B. W. Fox, and R. Raper, *J. Chem. Soc.* 2693 (1954).

also reported an instance where a 6-methyl-4-quinolizone fails to form a benzylidene derivative.

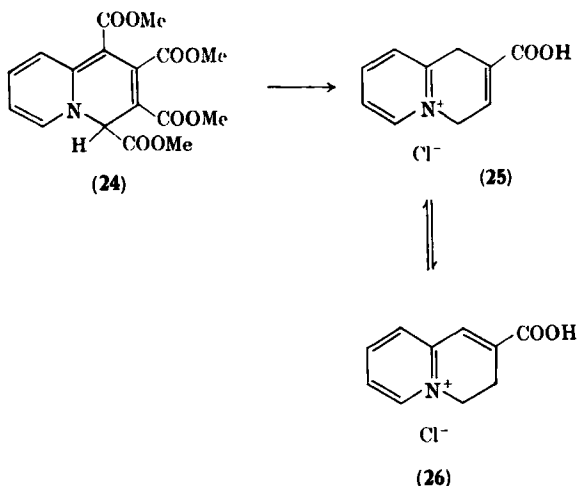
None of these methylquinolizinium derivatives forms an anhydro base.

D. ESTER HYDROLYSIS AND ESTER INTERCHANGE

Hydrolysis of quinolizinecarboxylic esters can be effected with acid or base. Acid hydrolysis can be effected selectively and stepwise. For instance, 1,3-dicarbethoxy-4-quinolizone can be hydrolyzed to 1-carbethoxy-3-carboxy-4-quinolizone with concentrated hydrochloric acid below 100°, ²³ but further heating at higher temperatures causes hydrolysis and decarboxylation of both ester groups to give 4-quinolizone. ¹⁸ Hydrolysis with alkali at room temperature affords the corresponding di-acid. ²⁹ Similar selective hydrolysis has also been observed with the 1,3-dicarbomethoxy ²³ and 1-carbomethoxy-3-carbethoxy derivatives. ¹⁸

Adams and Reifschneider ²² have reported ring opening and formation of 6-hydroxypyridine-2-crotonic acid by strong alkaline or acid hydrolysis of 6-hydroxy-4-quinolizone with ester groups in the 1- and 3-positions. However, hydrolysis with barium oxide affords the corresponding 1-carbethoxy-3-carboxy-6-hydroxy-4-quinolizone.

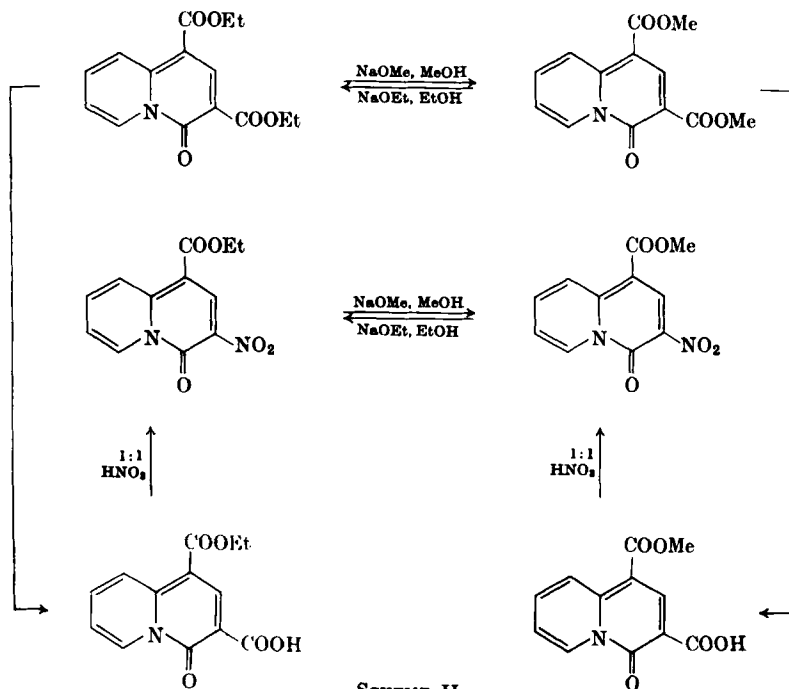
Recently Acheson *et al.* ³⁰ studied the hydrolysis of tetramethyl 4*H*-quinolizine-1,2,3,4-tetracarboxylate (24) in hydrochloric acid



²⁹ V. Boekelheide and W. G. Gall, *J. Org. Chem.* **19**, 499 (1954).

³⁰ R. M. Acheson, J. M. F. Gagan, and G. A. Taylor, *J. Chem. Soc.* 1903 (1963).

solution and reported the formation of 1,4-dihydro-2-carboxy-quinolinium chloride (**25**). This compound underwent base-catalyzed tautomerism to an isomeric derivative (**26**). The protonation of tetramethyl 4*H*-quinolizine-1,2,3,4-tetracarboxylate is reported to occur predominantly at the 3-position.³¹ Although formation of the 1,4-dihydro derivative on acid hydrolysis of the tetra-ester is rather surprising, Acheson *et al.*³⁰ have proposed a reasonable mechanism for this reaction.



SCHEME II

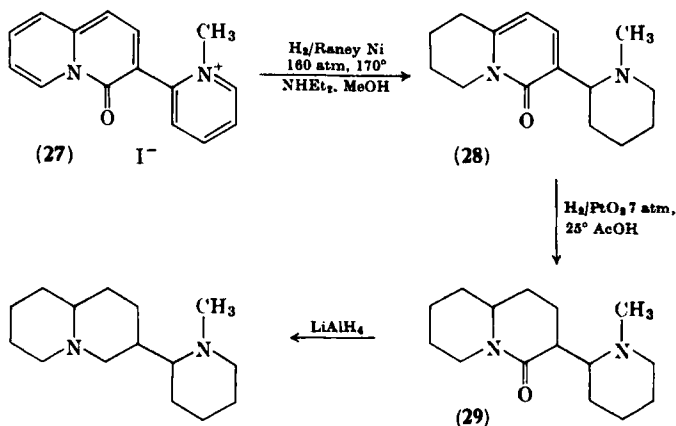
The esters of 1,3-dicarboxy-4-quinolizones show a tendency to undergo ester interchange on treatment with sodium alkoxides. For example, 1,3-dicarbethoxy-4-quinolizone on treatment with sodium methoxide in methanol affords the corresponding dicarbomethoxy derivative in high yield.²⁷ On treatment of the latter with sodium ethoxide, the original dicarbethoxy derivative is obtained. A similar observation was also made with the 1-carbethoxy-3-nitro-4-quinolizone as outlined in Scheme II.

³¹ R. M. Acheson and G. A. Taylor, *J. Chem. Soc.* 4600 (1960).

Ring contraction to form the indolizine ring system is another side-reaction in the alkaline hydrolysis of a quinolizine ester. Acheson *et al.*³⁰ have studied in detail the conversion of tetramethyl 4*H*-quinolizine-1,2,3,4-tetracarboxylate into the corresponding indolizine derivative.

E. OXIDATIONS AND REDUCTIONS

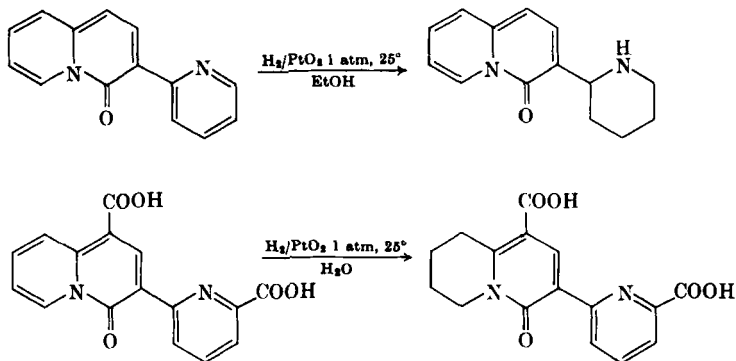
Just as in hydrolysis, hydrogenation of substituted quinolizines can also be carried out stepwise. Usually the first stage in hydrogenation is the saturation of the unsubstituted ring. Boekelheide and Lodge¹⁸ showed that in neutral medium an octahydro derivative was formed, whereas in acidic medium only the non-oxygenated ring was reduced. This observation has been confirmed by Bohlmann *et al.*³² for related quinolizones. Clemo *et al.*²⁸ studied the hydrogenation of 3-(2-pyridyl)quinolizin-4-one and observed an interesting pattern of saturation of the different rings under various conditions. The methiodide (27) of this compound in methanol in the presence of diethylamine



and Raney nickel, at 160 atmospheres and 170°, absorbs five moles of hydrogen to give 28. Further hydrogenation (7 atm) at 25° over platinum in acetic acid affords the fully reduced 4-ketoquinolizidine (29). When the non-oxygenated ring of the quinolizin-4-one is reduced the characteristic color and fluorescence of the quinolizone system disappears, whereas when the pyridine moiety is reduced this fluores-

³² F. Bohlmann, N. Ottawa, and R. Keller, *Ann. Chem.* **587**, 172 (1954).

cence persists. This fluorescence and color of quinolizone derivatives can be a good indication of which ring is reduced upon hydrogenation. Reduction in the presence of Adams' catalyst at 25° and atmospheric pressure in ethanol solution affects only the side-chain pyridine ring [Eq. (14)] and the resultant compound shows a light yellow color and

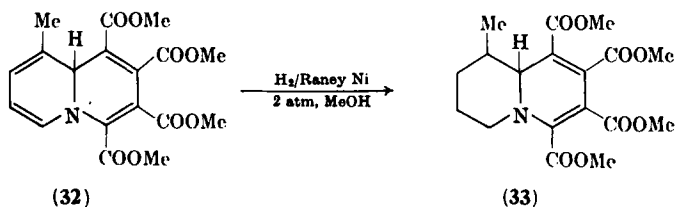


fluorescence. If carboxylic groups are present in the molecule, under the same conditions, the non-oxygenated ring is saturated [Eq. (15)] and the product shows no fluorescence.

Hydrogenation of 4*H*-quinolizine derivatives apparently gives rise to a different mode of saturation. Acheson and Taylor³¹ reduced tetramethyl 4*H*-quinolizine-1,2,3,4-tetracarboxylate (**30**) over Raney

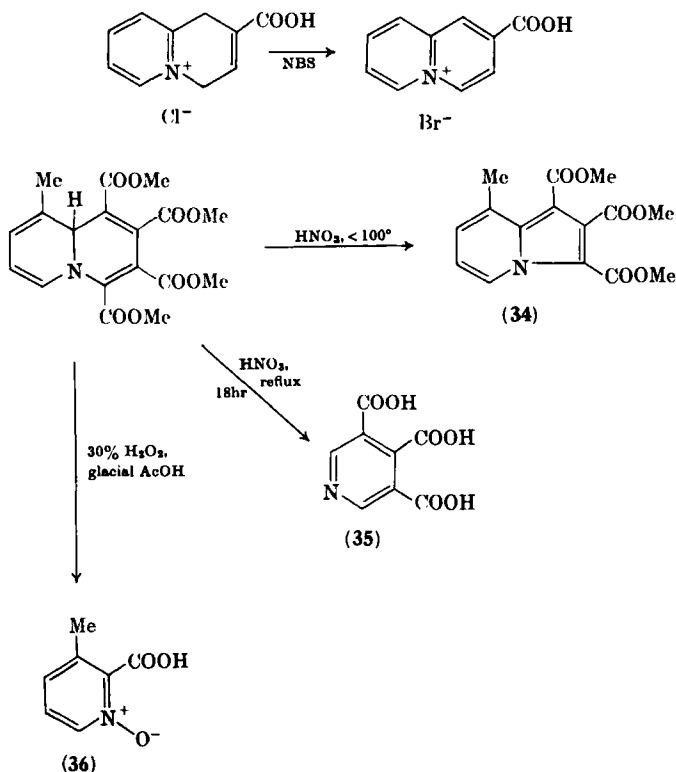


nickel in methanol at 25° and atmospheric pressure and obtained **31**. As mentioned in Section III, D, hydrogenation of **30** results in the formation of a 1,4-dihydro derivative from a 1,2-dihydro compound. However, hydrogenation under similar conditions of tetramethyl 9-methyl-9*aH*-quinolizine-1,2,3,4-tetracarboxylate (**32**) gave only the 1,2-dihydropyridine **33**; the ring carrying the methyl group was reduced.



Hydrogenation of thieno[2,3-*b*]quinolizinium bromide over Raney nickel in ethanol at two atmospheres of pressure affords 3-ethyl-quinolizidine with loss of sulfur from the nucleus.³³

Oxidation of quinolizines leads to a variety of products depending on the reagent and experimental conditions. Quinolizinium salts can be obtained from 4*H*-quinolizine derivatives by oxidation with



³³ M. Neeman, E. Krakauer, and Y. Shorr, *J. Am. Chem. Soc.* **79**, 4380 (1957).

bromine in methanol²⁶ or with *N*-bromosuccinimide.³⁰ Dihydroquinolizines can also be oxidized with the latter reagent to quinolizinium compounds [Eq. (16)]. Oxidation with nitric acid or chromic acid at lower temperatures results in ring contraction with the formation of indolizine derivatives (34). Under more drastic conditions, the same reagents lead to rupture of the ring with the formation of pyridinecarboxylic acids (35).^{26, 31} Treatment with 30% hydrogen peroxide in acetic acid also causes rupture of the ring with the formation of substituted pyridine-2-carboxylic acid 1-oxide (36).

IV. Spectra of Quinolizines

A. ULTRAVIOLET SPECTRA

A molecular orbital calculation of the ultraviolet spectrum of the quinolizinium cation has been made employing self-consistent field molecular orbitals of the parent hydrocarbon.³⁴ Of the four band positions calculated on this basis, only two have been observed. The calculated and observed values are given in Table IV.

TABLE IV
ULTRAVIOLET ABSORPTION BANDS OF THE QUINOLIZINIUM CATION

State and symmetry of quinolizinium ion	Transition energy, ν	
	Calculated	Observed
(B)	34900	30300
p (A)	41300	44000
(B)	60700	not yet observed
(A)	63000	not yet observed

The ultraviolet absorption spectra have been used to distinguish between the tautomers obtained by addition of dimethyl acetylenedicarboxylate to pyridines. The 4*H*-quinolizines show a band around 265 $m\mu$ which is missing from the spectra of the 9*aH*-quinolizines. Acheson and Taylor²⁶ have successfully used this information to settle the constitution of the stable and labile adducts obtained by the action of acetylenedicarboxylic esters on pyridines. The ultraviolet spectra of the stable adducts formed by the above methods show

³⁴ T. E. Peacock, *J. Chem. Soc.* 3645 (1959).

considerable alteration on the addition of acid. The stable adducts are basic to perchloric acid, but the labile adducts are not. The change in the spectrum clearly indicates that protonation occurs at the 3-position in the stable compounds since the spectrum of the protonated species resembles that of the 3,4-dihydroquinolizinium cation. The spectral maxima of the quinolizinium derivatives representative of the different types are listed in Table V.

TABLE V
ULTRAVIOLET SPECTRAL DATA

Compound	Solvent	λ_{\max} , m μ	$\log_{10} \epsilon$	Refer- ence
Quinolizinium iodide	H ₂ O	226	4.25	4
		272	3.42	
		283	3.47	
		310	4.03	
		316.5	3.98	
		325.5	4.23	
Tetramethyl 4 <i>H</i> -quinolizine-1,2,3,4-tetracarboxylate	MeOH	259	3.99	26
		306	4.20	
		344.5	4.05	
		441	4.05	
Tetramethyl 9 <i>aH</i> -quinolizine-1,2,3,4-tetracarboxylate	MeOH	280	4.15	26
		427	3.70	
Tetramethyl 6,7,8,9-tetrahydro-2 <i>H</i> -quinolizine-1,2,3,4-tetracarboxylate	MeOH	225	4.06	
		286	4.18	
		373	3.96	
Tetramethyl 9-methyl-6,7,8,9-tetrahydro-9 <i>aH</i> -quinolizine-1,2,3,4-tetracarboxylate	MeOH	231	4.08	26
		286	4.17	
		411	3.46	
4-Quinolizone	—	245	—	37
		380	—	
6,7,8,9-Tetrahydro-4-quinolizone	MeOH	235	3.76	32
		311	3.86	

TABLE V—*continued*

Compound	Solvent	λ_{\max} , m μ	$\log_{10} \epsilon$	Refer- ence
1,3-Dicarbethoxy-4-quinolizone	MeOH	265	4.18	32
		342.5	3.98	
		395	4.21	
1,3-Dicarbethoxy-6,7,8,9-tetrahydro-4-quinolizone	MeOH	265	4.22	32
		333	4.02	
2-Carboxyquinolizinium bromide	MeOH	269	3.51	30
		280	3.46	
		294	3.38	
		328	4.03	
		339	4.18	
2-Carboxy-1,4-dihydroquinolizinium chloride	—	267	3.66	30
2-Carboxy-3,4-dihydroquinolizinium chloride	—	252.5	3.86	30
		313.5	4.08	
1,2-Dihydroquinolizinium picrate	E + OH	315	3.94	10
		329	4.20	
		357	4.15	
1-Hydroxyquinolizinium bromide	—	237	4.15	21
		345	4.17	
3-Hydroxyquinolizinium bromide	—	227	4.39	21
		246	4.37	
		330	3.90	
		340	3.92	

B. INFRARED SPECTRA

The infrared spectrum of 4-quinolizone shows an amide carbonyl band, which serves to emphasize the aromatic character in the system, and its position (6.06 μ) emphasizes the greater single bond contribution of the amide carbonyl due to resonance. The introduction of

substituents carrying opposing dipoles tends to shift this band to shorter wavelengths as is observed for 1-nitro-, 3-nitro-, and 1,3-dinitro-4*H*-quinolizones where the amide carbonyl maximum occurs at 5.90, 5.875, and 5.80 μ , respectively. Similarly, introduction of groups capable of forming hydrogen bonds with the carbonyl group tends to lengthen it and causes the maximum to shift to longer wavelength. 3-Amino- and 3-carboxy-4*H*-quinolizones absorb in the region 6.125 and 6.10 μ , respectively. Such sensitivity of the amide carbonyl band has been reported³⁵ for the pyridone series and may be used to locate the positions of these substituents.

TABLE VI
POSITION OF THE AMIDE CARBONYL BAND IN VARIOUS QUINOLIZONES

Compound	Amide carbonyl band, μ
4-Quinolizone	6.06
1-Carbethoxy-3-nitro-4-quinolizone	5.90
3-Nitro-4-quinolizone	5.875
1-Nitro-4-quinolizone	5.90
1,3-Dinitro-4-quinolizone	5.80
1-Carbethoxy-3-amino-4-quinolizone	6.125
1-Carbethoxy-3-carboxy-4-quinolizone	6.10

Note Added in Proof (see page 304)

Acetyl groups are also readily displaced by nitro groups.²⁷ Thus, by the action of concentrated nitric acid at 25°, 1,3-diacetyl-, 1-acetyl-3-carbethoxy-, and 3-acetyl-1-carbethoxy-4-quinolizone are converted into the corresponding nitro derivatives. Carboxyl groups are also displaced by bromine; for example, 1,3-dibromo- and 3-bromo-1-carbethoxy-4-quinolizone have been prepared by refluxing the appropriate carboxyquinolizone with bromine in acetic acid.²⁷

³⁵ H. Tomisawa and T. Agatsuma, *Yakugaku Zasshi* **82**, 25 (1962).

Advances in Pyrrolizidine Chemistry

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Academy of Sciences, Moscow, U.S.S.R.*

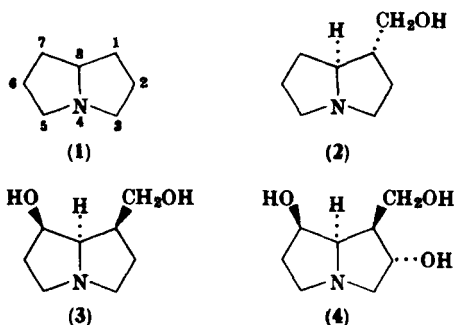
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I. Introduction

Pyrrolizidine (1) and its derivatives have attracted the attention of chemists during the last two or three decades because this bicyclic system occurs in a number of alkaloids from various families of Compositae, Boraginaceae, Leguminosae, etc. Structural analysis of these substances, study of their reactions, and attempted syntheses have afforded considerable information concerning the chemistry of this class of compounds. Although the field has been covered by a

number of previous reviews¹⁻⁵ evidence obtained during the last few years now enables critical discussion of some new aspects of pyrrolizidine chemistry. The previous reviewers tended to concentrate on advances in the isolation and structural analysis of naturally occurring representatives of the series, hence it seemed advisable to emphasize the stereochemical and synthetic studies in the present survey.

Pyrrolizidine alkaloids are usually composed of two moieties—the pyrrolizidine alcohol and a carboxylic (usually hydroxy) acid, which are combined by an ester linkage. The pyrrolizidine moieties may appear as monohydric (trachelanthamidine, **2**), dihydric (platynecine, **3**), or trihydric alcohols (rosmarinecine, **4**).



Monocarboxylic [as in heliotrine (**5**) and trachelanthamine (**6**)] and dicarboxylic acids [in senecionine (**7**) and thesine (**8**)] are found among the carboxylic acid moieties. All the pyrrolizidine alkaloids afford pyrrolizidine alcohols under conventional conditions of ester hydrolysis. Formerly, these alcohols were used as starting materials for all the studies dealing with pyrrolizidine chemistry; synthetic approaches have now been developed. Some pyrrolizidine alcohols, and other derivatives like 1-methylenepyrrolizidine, occur in plants in the free state, forming the special group of the so-called "non-ester" pyrrolizidine alkaloids.

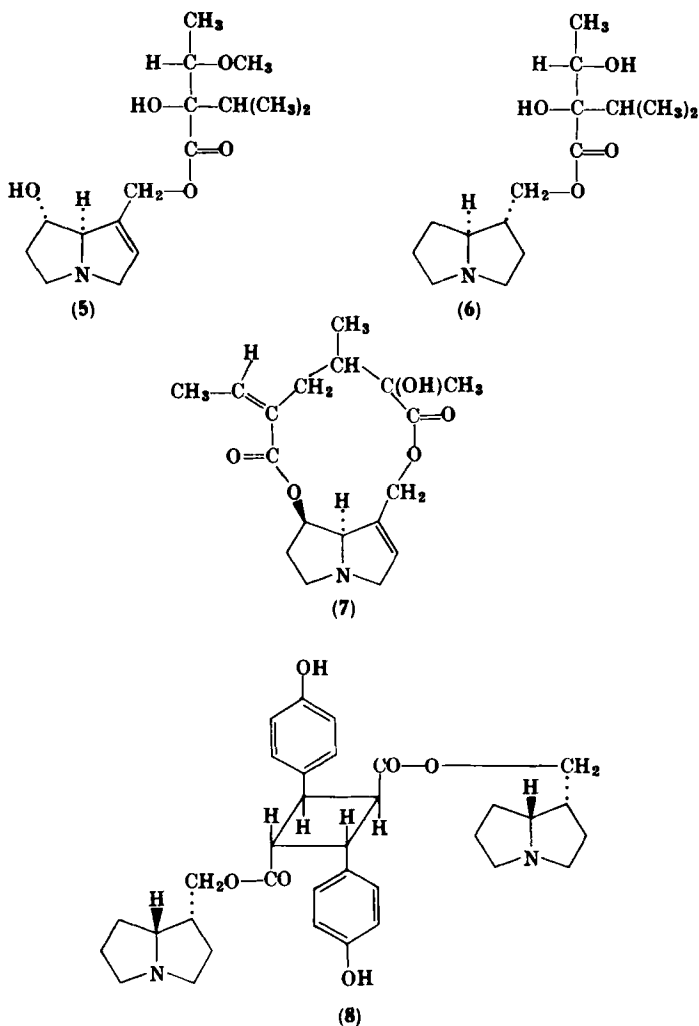
¹ F. L. Warren, *Fortschr. Chem. Org. Naturstoffe* **12**, 198 (1955).

² R. Adams and M. Gianturco, *Angew. Chem.* **69**, 5 (1957).

³ C. C. J. Culvenor, in "Symposium on Current Trends in Heterocyclic Chemistry" (A. Albert, G. M. Badger, and C. W. Shoppee, eds.), p. 103. Butterworths, London (1958).

⁴ N. J. Leonard, in "The Alkaloids" (R. H. F. Manske, ed.), Chapter 3, Vol. 6. Academic Press, New York, London, 1960.

⁵ H. J. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960." Akademie-Verlag, Berlin, 1961.



The present review covers the literature summarized in *Chemical Abstracts* up to 1962, although more recent publications are mentioned occasionally.

II. The Synthesis of Pyrrolizidine Derivatives

The first synthetic approaches to compounds containing the pyrrolizidine system were made as soon as the complete structures of a number

of pyrrolizidine alkaloids were established. However, only the simplest alkylpyrrolizidines were available synthetically until some 4–5 years ago when synthetic routes to functionally substituted pyrrolizidines, and, *inter alia*, to natural pyrrolizidine alcohols, were developed.

There are at present several synthetic methods of differing scope and practical value. These can be summarized in the following manner:

(A) Pyrrolizidine syntheses involving cyclization of alkyl-substituted *N*-halogenopyrrolidines.

(B) Cyclization of halides and halogenoamines, and intramolecular cyclodehydration.

(C) Intramolecular acylation of amino acids and their derivatives.

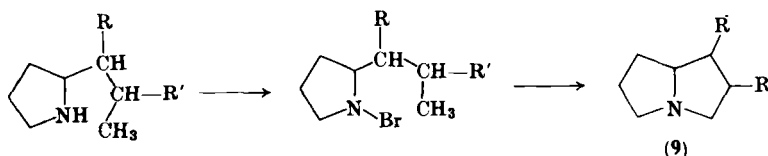
(D) Reductive cyclization of nitropimelates and related compounds.

(E) Dieckmann condensation of pyrrolidine derivatives.

(F) Other reactions.

A. CYCLIZATION OF ALKYL-SUBSTITUTED *N*-HALOGENOPYRROLIDINES

The first synthetic method which afforded the pyrrolizidine system was proposed by Menshikov. The approach was based on the reaction of *N*-halogenoamines studied by Hofmann,⁶ i.e. cyclization of 2-alkyl-*N*-bromopyrrolidines in the presence of concentrated sulfuric acid.



Using this method Menshikov obtained 1-methyl- (9; R = CH₃, R' = H)⁷ and 2-methyl-pyrrolizidine (9; R = H, R' = CH₃),⁸ and Šorm and Brandejs synthesized unsubstituted pyrrolizidine (9; R = R' = H).⁹ The method has until recently been of only historical importance because of the very poor yields. However, in 1960 Schmitz and Muraw-

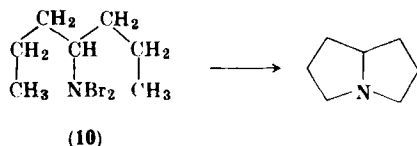
⁶ A. W. Hofmann, *Ber.* **18**, 109 (1885).

⁷ G. P. Menshikov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* 1035 (1937); *Chem. Abstr.* **32**, 2944 (1938).

⁸ G. P. Menshikov, *Ber.* **69**, 1802 (1936).

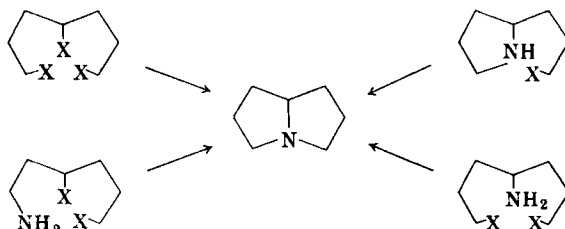
⁹ F. Šorm and J. Brandejs, *Collection Czech. Chem. Commun.* **12**, 444 (1947); *Chem. Abstr.* **43**, 2988d (1949).

ski^{10, 11} proposed an effective photochemical modification of the same reaction: *N,N*-dibromo-4-aminoheptane (10), when irradiated in sulfuric acid with ultraviolet light, affords pyrrolizidine in 34% yield.



B. CYCLIZATION OF HALIDES AND HALOGENOAMINES, AND INTRAMOLECULAR CYCLODEHYDRATION

This method is of rather wide importance; its scope extends to include the synthesis of various alkylpyrrolizidines and, as shown recently, some functional pyrrolizidine derivatives. It can be outlined by several routes (see Scheme 1).



SCHEME 1

The choice of one or other route depends on the availability of the starting halide. The method was applied originally by Prelog and Heimbach¹² to the synthesis of unsubstituted pyrrolizidine. Malonic ester afforded diethyl bisethoxypropylmalonate (11) by two successive alkylations with γ -ethoxypropyl bromide, and, after hydrolysis and decarboxylation, bisethoxypropylacetic acid (12) was obtained. The acid was converted into amine 13 by Curtius rearrangement; the amine was then transformed into 4-amino-1,7-dibromoheptane (14), which was subjected to cyclization in alkaline solution to give pyrrolizidine.

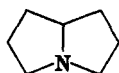
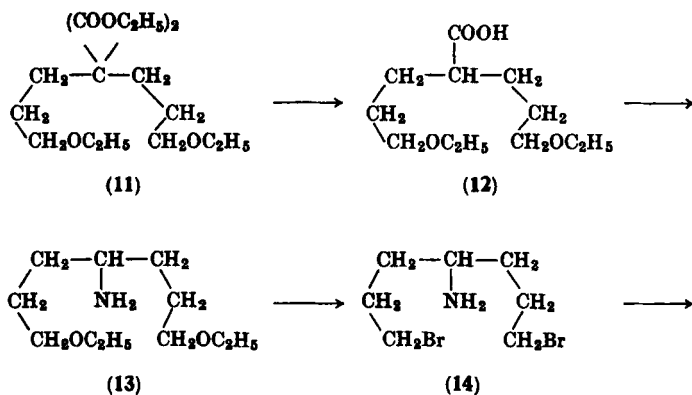
The synthesis of 1-methylpyrrolizidine¹³ was accomplished starting with 2-cyano-4-phenoxybutane. The compound was treated with γ -ethoxypropylmagnesium bromide, and the ketone (15) obtained was

¹⁰ E. Schmitz and D. Murawski, *Chem. Ber.* **93**, 754 (1960).

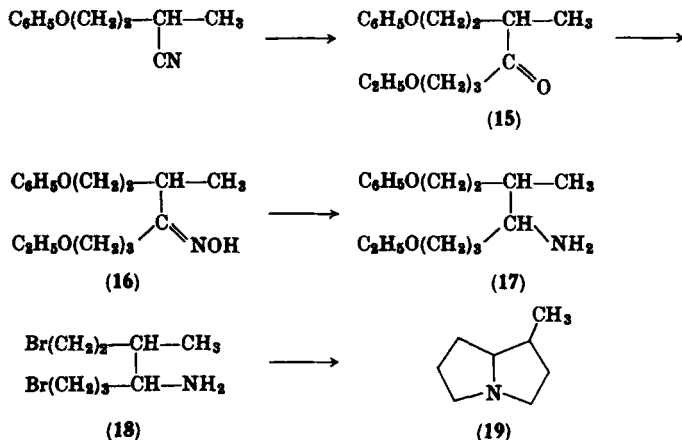
¹¹ E. Schmitz, *Angew. Chem.* **73**, 23 (1961).

¹² V. Prelog and S. Heimbach, *Ber.* **72**, 1101 (1939).

¹³ V. Prelog and E. Zalan, *Helv. Chim. Acta* **27**, 531 (1944).



converted via oxime **16** into amine **17**. Heating this amine with concentrated hydrobromic acid resulted in the formation of 3-methyl-4-amino-1,7-dibromoheptane (**18**), which afforded 1-methylpyrrolizidine (**19**) on treatment with dilute alkali.

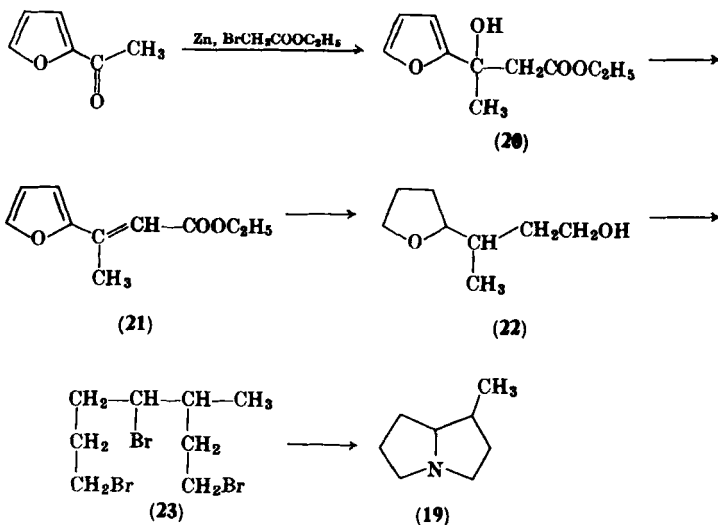


Furan derivatives are sometimes convenient starting materials in this group of syntheses.¹⁴ For example, catalytic hydrogenation of

¹⁴ (a) F. Šorm and Z. Arnold, *Collection Czech. Chem. Commun.* **12**, 467 (1947); *Chem. Abstr.* **43**, 214 (1949); (b) R. Seiwerth, *Arkiv Kemi* **23**, 77 (1951); *Chem. Abstr.* **45**, 10183h (1951).

furylpropylamine leads to tetrahydrofurylpropylamine, which can be converted via its dibromide to pyrrolizidine by intramolecular alkylation. Pyrrolizidine was also obtained from tetrahydrofurylpropanol, the latter affording 1,4,7-tribromoheptane on heating with concentrated hydrobromic acid; the tribromoheptane undergoes ring closure on heating with methanolic ammonia at 130–140°.

2-Acetylfuran served as a starting compound in a synthesis of 1-methylpyrrolizidine.¹⁵ The substance was converted into hydroxyester **20** by a Reformatski reaction. The hydroxyester, via the unsaturated ester **21**, was converted into ethyl 2-(α -tetrahydrofuryl)-butyrate. The latter was reduced to **22**. Ring closure to give 1-methylpyrrolizidine was effected via the corresponding tribromide (**23**). The final product was identical with racemic heliotridane. Analogous treatment of other furan derivatives led to 2-¹⁶ and 3-methylpyrrolizidine.¹⁷



Another route to pyrrolizidine derivatives starting from furan derivatives was devised by Ponomarev *et al.*^{18, 19} The method is based

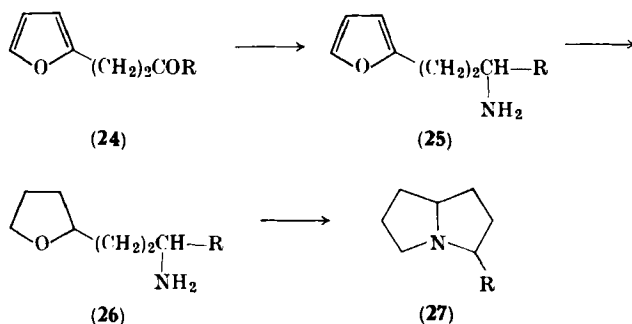
¹⁵ R. Seiwerth and B. Orescanin-Majhofer, *Arkiv Kemi* **24**, 53 (1952); *Chem. Abstr.* **49**, 295d (1955).

¹⁶ B. Orescanin-Majhofer and R. Seiwerth, *Arkiv Kemi* **25**, 131 (1953); *Chem. Abstr.* **49**, 2415d (1955).

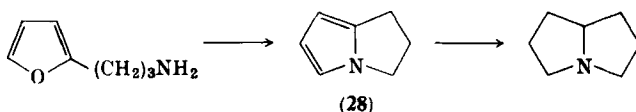
¹⁷ B. Orescanin-Majhofer and R. Seiwerth, *Monatsh. Chem.* **83**, 1298 (1952).

¹⁸ A. A. Ponomarev, N. P. Maslennikova, N. V. Alakhina, and A. P. Krivenko, *Dokl. Akad. Nauk SSSR* **131**, 1355 (1960); *Chem. Abstr.* **54**, 21032c (1960).

on catalytic dehydration of tetrahydrofurylamines over thorium oxide at *ca.* 300° and can be regarded as a special case of the known reaction of tetrahydrofuran with amines, leading to pyrrolidine derivatives.



Hydrogenation of ketones of type **24** at elevated pressure and temperature over Raney nickel in alcoholic ammonia gives rise to the corresponding amines (**25**), the latter yielding *N*-acetylaminotetrahydrofurans on acetylation and hydrogenation in dioxane over Raney nickel at 100 atm and 80–120°. The aminotetrahydrofuran **26** can be converted into a pyrrolizidine (**27**) by dehydration over alumina. The method was also applied to the synthesis of 2,3-cyclohexanopyrrolizidine. It should be noted that ring closure to form the pyrrolizidine bicyclic system can also be effected by catalytic dehydration of furylpropylamine.⁹ The first step in this reaction involves the formation of 1,2-trimethylenepyrrole (**28**); hydrogenation of **28** over platinum affords pyrrolizidine.

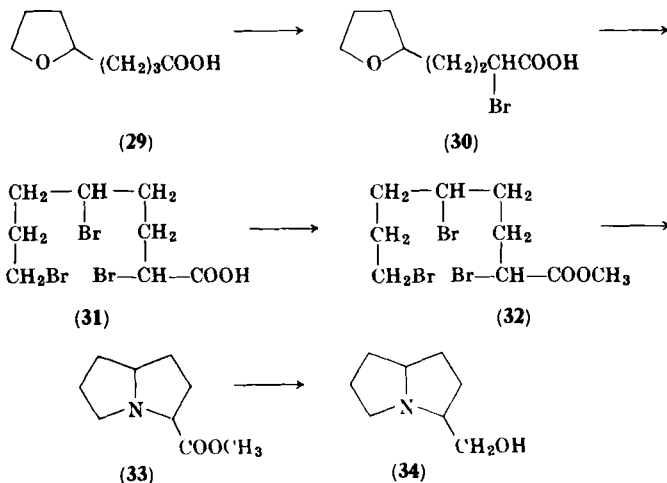


Intramolecular alkylation of the amino group has been applied more recently to the synthesis of functionally substituted pyrrolizidine derivatives. For example, Seiwerth and Djokic²⁰ reported the synthesis of 3-substituted pyrrolizidines. γ -Tetrahydrofurylbutyric acid, via

¹⁹ A. A. Ponomarev and I. M. Skvortsov, *Zh. Obshch. Khim.* **32**, 97 (1962); *Chem. Abstr.* **57**, 12409d (1962).

²⁰ R. Seiwerth and S. Djokic, *Croat. Chem. Acta* **29**, 403 (1957); *Chem. Abstr.* **53**, 16108g (1959).

the corresponding α -bromo derivative (30), was converted by heating with concentrated hydrobromic acid into the tribromo acid 31. The methyl ester of this acid (32) gave rise to methyl pyrrolizidine-3-carboxylate (33), which was subsequently reduced to 3-hydroxymethylpyrrolizidine (34) with lithium aluminum hydride. This

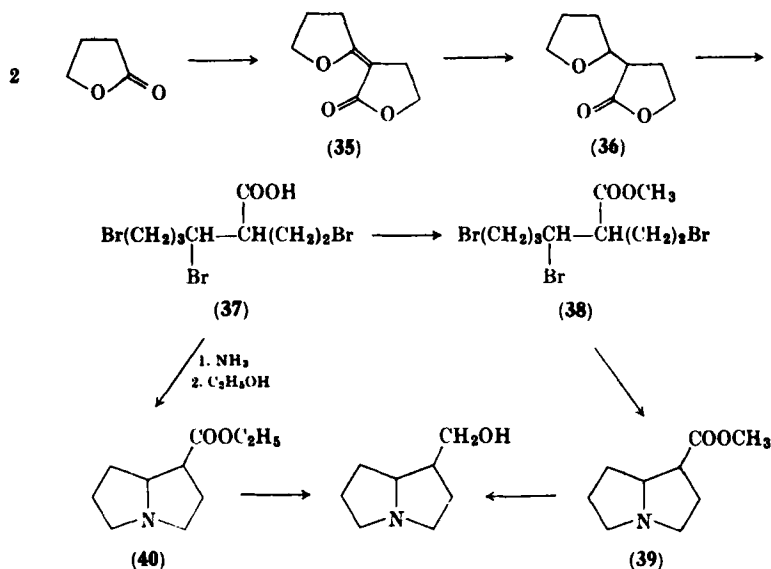


approach was applied later by Kochetkov *et al.* to the synthesis of the stereoisomeric 1-hydroxymethylpyrrolizidines, trachelanthamidine and isoretronecanol, which are the basic moieties present in some naturally occurring alkaloids. A convenient synthesis of trachelanthamidine starts from γ -butyrolactone.²¹ 3-(2-Tetrahydrofurylidene)-butyrolactone (35), obtained by condensation of γ -butyrolactone in the presence of sodium methoxide,^{22, 23} was converted by hydrogenation at 6 atm over Raney nickel into the dihydro derivative (36), which afforded the tribromo acid 37 on heating with concentrated hydrobromic acid. The tribromo ester underwent cyclization on heating with methanolic ammonia at 130–140° to give methyl pyrrolizidine-1-carboxylate (39). The latter was reduced with lithium aluminum hydride to 1-hydroxymethylpyrrolizidine. The major product of this reaction appeared to be (\pm)-trachelanthamidine, but it was very

²¹ N. K. Kochetkov, A. M. Likhoshervstov and E. J. Budowsky, *Khim. Nauka i Promy.* **4**, 678 (1959); *Zh. Obshch. Khim.* **30**, 2077 (1960); *Chem. Abstr.* **55**, 7386i (1961).

²² R. Fittig and K. T. Strom, *Ann. Chem.* **267**, 196 (1892).

²³ E. Spencer and L. Wright, *J. Am. Chem. Soc.* **63**, 1281 (1941).

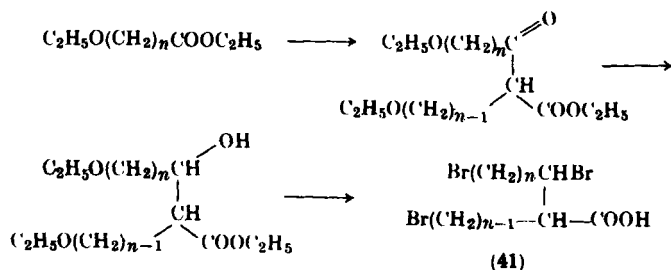


difficult to isolate from the mixture which also contained the diastereoisomer, isoretronecanol. The disadvantage of this method is the formation of large amounts of by-products during cyclization of the tribromo ester (38) to give 39. The yield was considerably increased by cyclizing the acid 37 instead of the ester²⁴; the pyrrolizidine-1-carboxylic acid formed was isolated as its ethyl ester (40). The authors obtained a good yield of the racemic pyrrolizidine-carboxylates, which could be easily separated, as picrates, into ethyl (±)-trachelanthamidinate and ethyl (±)-isoretronecanolate. Reduction of the racemic mixture (40) with lithium aluminum hydride resulted in the formation of 1-hydroxymethylpyrrolizidine, which was separated into two racemates, (±)-trachelanthamidine and (±)-isoretronecanol, via their picrates. The mixture of racemic bases could be separated by thin-layer chromatography on alumina.²⁵ A general method for preparation of the starting tribromo acids was developed^{24, 26}; its main steps are outlined in Scheme 2.

²⁴ A. M. Likhosherstov, L. M. Likhosherstov, and N. K. Kochetkov, *Zh. Obshch. Khim.* **33**, 1801 (1963).

²⁵ K. Babor, J. Ježo, V. Kalač, M. Karvaš, and K. Tihlárík, *Chem. Zvesti* **15**, 721 (1961); *Chem. Abstr.* **58**, 5744b (1963).

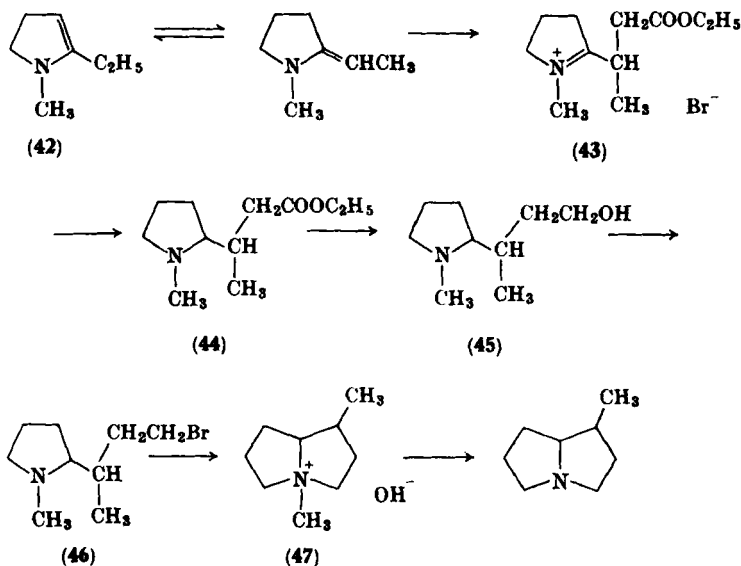
²⁶ N. K. Kochetkov, A. M. Likhosherstov, and L. M. Likhosherstov, *Zh. Vses. Khim. Obshchestva im. D. I. Mendeleeva* **5**, 109 (1960); *Chem. Abstr.* **54**, 21099i (1960).



SCHEME 2

Tribromo acids of this type (41) can also be used for the synthesis of quinolizidine and other 1-azabicyclic alkanes with functional substituents.

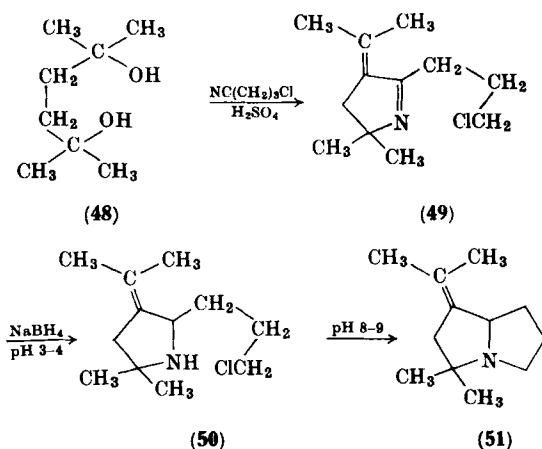
A very interesting modification of method *B* was applied to the stereospecific synthesis of (\pm)-pseudoheliotridane.²⁷ Condensation of ethyl bromoacetate with 1-methyl-2-ethyl-4,5-dihydropyrrole (42) afforded the quaternary salt 43, which was reduced, without isolation, with formic acid to give ethyl β -(*N*-methyl-2-pyrrolidyl)butyrate (44). The amino alcohol (45), obtained by reduction of 44 with lithium



²⁷ O. Červinka, *Collection Czech. Chem. Commun.* **24**, 1880 (1959); *Chem. Abstr.* **52**, 11004f (1958).

aluminum hydride, was converted via the corresponding bromide (46) into the quaternary base 47. Pyrolysis of the quaternary base acetate afforded (\pm)-pseudoheliotridane. Application of this scheme to the asymmetric synthesis of pseudoheliotridane from (+)-bornyl bromoacetate was unsuccessful.

A new synthesis of pyrrolizidine, which is based on the reaction of bis-tertiary glycols with ω -chloronitriles, was reported by Meyers and Libano.²⁸ The method involves three steps: (a) condensation of 2,5-dimethyl-2,5-hexanediol (48) with 4-chlorobutyronitrile in the presence of sulfuric acid to give a derivative of Δ^1 -pyrroline (49), (b) reduction of 49 with sodium borohydride to give the corresponding pyrrolidine (50), and (c) intramolecular cyclization of the pyrrolidine in the presence of alkali to give the pyrrolizidine derivative 51. The three-step synthesis was performed without isolation of the intermediate products.



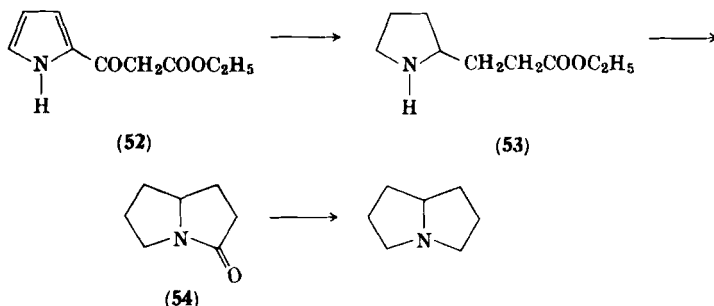
C. INTRAMOLECULAR ACYLATION OF AMINO ACIDS

A number of syntheses of pyrrolizidine derivatives are based on cyclization of amino acids such as β -(pyrrolidin-2-yl)propionic acid, 4-aminopimelic acid, and their homologues to give 3-oxo- and 3,5-dioxo-pyrrolizidines. Reduction of these cyclic amides leads to pyrrolizidines.

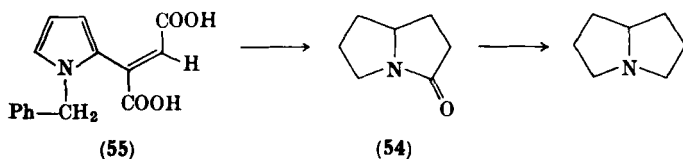
Several modifications of this route to pyrrolizidine have been

²⁸ A. J. Meyers and W. J. Libano, *J. Org. Chem.* **26**, 4399 (1961).

reported which differ in the method of preparation of the starting amino acids. Galinovsky and Reichard²⁹ started with the pyrrole ketoester **52**, which was reduced catalytically to ethyl β -(pyrrolidin-2-yl)propionic acid (**53**) and then converted into 3-oxopyrrolizidine (**54**) by heat. Electrolytic reduction of **52** afforded pyrrolizidine.



Another synthesis was reported by Červinka *et al.*³⁰ Hydrogenation of 1-benzyl-2-pyrrolylfumaric acid (**55**) in the presence of Raney nickel at 140 atm and 150° in methanol proceeded with simultaneous decarboxylation to result in a high yield of 3-oxopyrrolizidine (**54**), which was reduced with lithium aluminum hydride to pyrrolizidine.



The synthesis of pyrrolizidine developed by Lukeš and Šorm³¹ and by Micheel and Flitsch³² starts with furylacrylic acid (**56**) which is converted by the Markwald reaction into γ -ketopimelic acid (**57**). The carbonyl group in **57** is replaced by an amino group via the oxime or by the Leuckart-Wallach reaction; this substitution results immediately in the formation of the lactam **58**, which can be converted by heat into 3,5-dioxopyrrolizidine (**59**). The latter compound yields pyrrolizidine

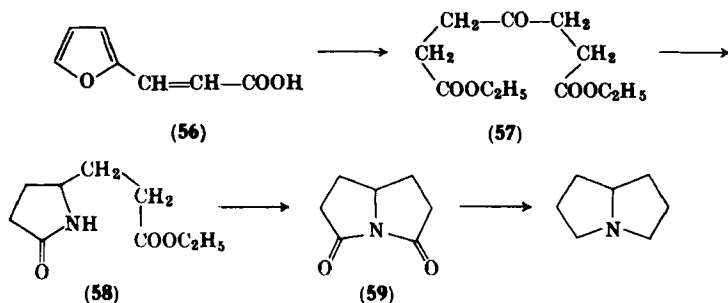
²⁹ F. Galinovsky and A. Reichard, *Ber.* **77**, 138 (1944).

³⁰ O. Červinka, K. Pelz, and J. Jirkowský, *Collection Czech. Chem. Commun.* **26**, 3116 (1961); *Chem. Abstr.* **56**, 10204d (1962).

³¹ R. Lukeš and F. Šorm, *Collection Czech. Chem. Commun.* **12**, 278 (1947); *Chem. Abstr.* 557e (1948).

³² F. Micheel and W. Flitsch, *Chem. Ber.* **88**, 509 (1955).

on treatment with lithium aluminum hydride³³ or on electrolytic reduction. 3,5-Dioxopyrrolizidine was also obtained by Micheel and Albers³³ upon heating 4-aminopimelic lactam with acetic anhydride (cf. ref. 34).



Lukeš and Janda³⁵ obtained 1-methylpyrrolizidine by a similar route; rather surprisingly the product appeared to be pure (\pm)-pseudoheliotridane.

Šorm and Beranek³⁶ used an intramolecular acylation in their synthesis of 1-azoniumtricyclo[3.3.3.0]undecane (66). Condensation of nitromethane with acrylonitrile in the presence of an alkaline catalyst resulted in the formation of tris-(2-cyanoethyl)nitromethane (60), which afforded the triethyl ester 61 on hydrolysis followed by esterification. The ester was reduced catalytically to give a pyrrolidone (62). The derivative (62) gave rise to 8-(β -carboethoxyethyl)-3,5-dioxopyrrolizidine (63) on heating. Reduction of 63 resulted in the formation of 8-(γ -hydroxypropyl)pyrrolizidine (64). Replacement of the hydroxy group by bromine (65), followed by cyclization, afforded the tricyclic compound 66.

Intramolecular acylation was recently applied to the synthesis of diastereoisomeric 1-hydroxymethylpyrrolizidines.³⁰ Condensation of *N*-benzylpyrrole with acetylenedicarboxylic acid³⁷ gave (1-benzyl-

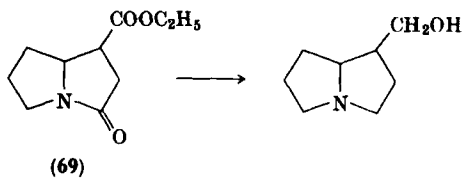
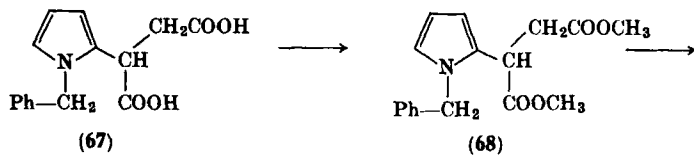
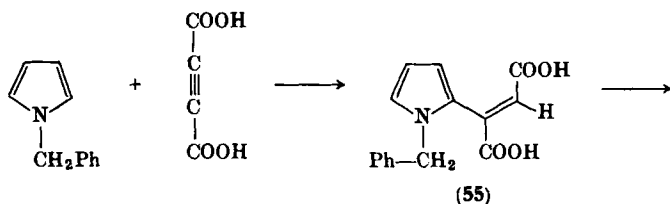
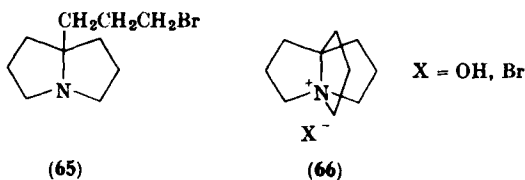
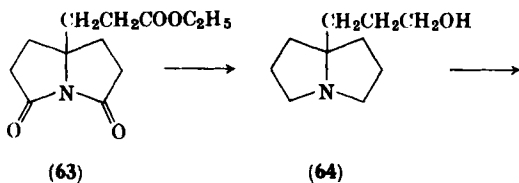
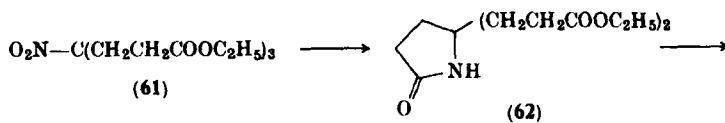
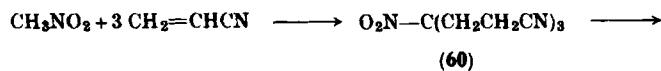
³³ F. Micheel and H. Albers, *Ann. Chem.* **581**, 225 (1953).

³⁴ N. J. Leonard, L. Hruda, and F. Long, *J. Am. Chem. Soc.* **69**, 690 (1947); J. M. Pouchol, *Chim. Mod.* **7**, N51, 311 (1962); J. Colonge and J. M. Pouchol, *Bull. Soc. Chim. France* 589 (1962).

³⁵ R. Lukeš and M. Janda, *Chem. Listy* **52**, 450 (1958); *Chem. Abstr.* **53**, 4252h (1959); *Collection Czech. Chem. Commun.* **24**, 599 (1959); *Chem. Abstr.* **53**, 13133b (1959).

³⁶ F. Šorm and J. Beranek, *Collection Czech. Chem. Commun.* **19**, 298 (1954); *Chem. Abstr.* **49**, 292c (1955).

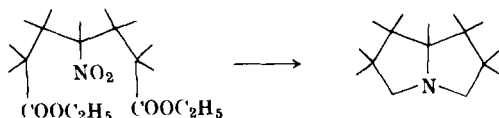
³⁷ L. Mandell and W. A. Branchard, *J. Am. Chem. Soc.* **79**, 2343, 6198 (1957).



pyrrol-2-yl)fumaric acid (55), which was transformed into (1-benzylpyrrol-2-yl)succinic acid (67) by hydrogenation over palladium on charcoal. Hydrogenation of the dimethyl ester (68) in the presence of the above-mentioned catalyst in methanolic hydrogen chloride yielded 1-carbomethoxy-3-oxopyrrolizidine (69). Reduction of (69) with lithium aluminum hydride gave rise to a mixture of diastereoisomeric 1-hydroxymethylpyrrolizidines, which contained (\pm)-trachelanthamidine and (\pm)-isoretronecanol in a 9:1 mole ratio as revealed by gas chromatography. The predominating isomer, purified as the picrate, was resolved using dibenzoyltartaric acid; the dextrorotatory isomer appeared to be identical with the alkaloid laburnine.

D. REDUCTIVE CYCLIZATION OF NITROPIMELATES AND RELATED COMPOUNDS

This method is very convenient for the synthesis of the simplest alkylpyrrolizidines. It is based on hydrogenation of 4-nitropimelates.^{34, 38-41} The starting nitropimelates are prepared by a two-step



condensation of various aliphatic nitro compounds with α,β -unsaturated carboxylates in the presence of a basic catalyst (amines, Triton B, etc.). Depending on the activity of the double bond of the esters involved and on the conditions of synthesis, one obtains addition products with one or two unsaturated ester residues per nitro residue. The 1:1 addition products can be condensed with other α,β -unsaturated esters to give various homologues of 4-nitropimelic acid. The latter are subjected to drastic hydrogenation conditions (250°, 300 atm) in the presence of copper chromite. Hydrogenation can also be performed stepwise: the nitro group can be reduced in the presence of platinum at 25° under low pressure and the product subjected to reductive cyclization. Combining various nitro compounds and α,β -

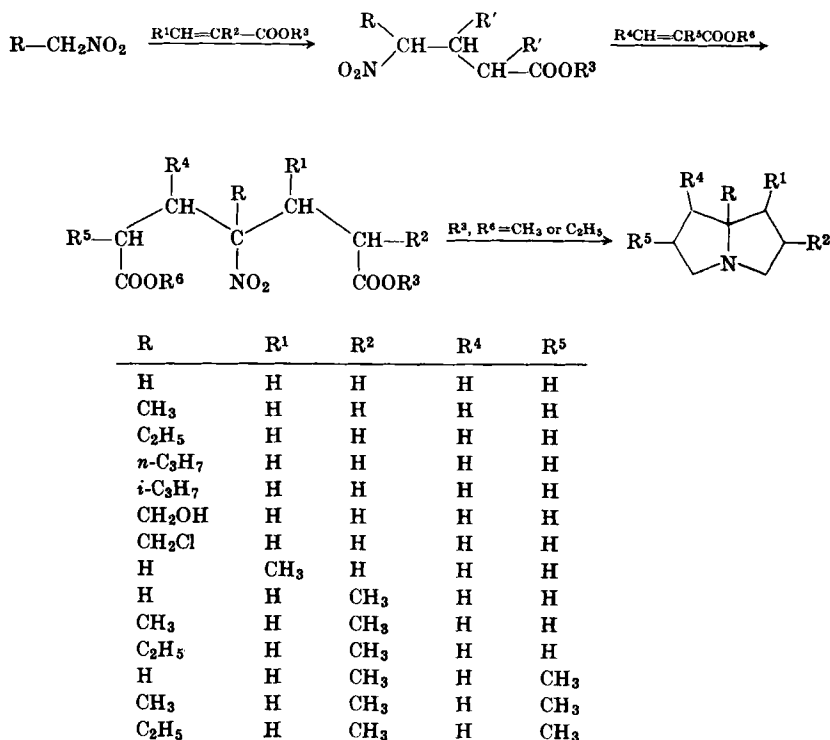
³⁸ N. J. Leonard and K. Beck, *J. Am. Chem. Soc.* **70**, 2504 (1948).

³⁹ N. J. Leonard and D. Felley, *J. Am. Chem. Soc.* **71**, 1758 (1949).

⁴⁰ N. J. Leonard and G. Shoemaker, *J. Am. Chem. Soc.* **71**, 1760 (1949).

⁴¹ N. J. Leonard and G. Shoemaker, *J. Am. Chem. Soc.* **71**, 1762 (1949); N. J. Leonard, D. Felley, and E. Nicolaides, *J. Am. Chem. Soc.* **74**, 1700 (1952).

unsaturated carboxylates, it is possible to obtain various alkyl-pyrrolizidines according to the tabulation given in Scheme 3.



SCHEME 3

Another interesting modification of the method is the reductive cyclization of ketodiester oximes. This modification considerably extends the scope of the method and makes available other 1-azabicycloalkanes besides pyrrolizidines.⁴²

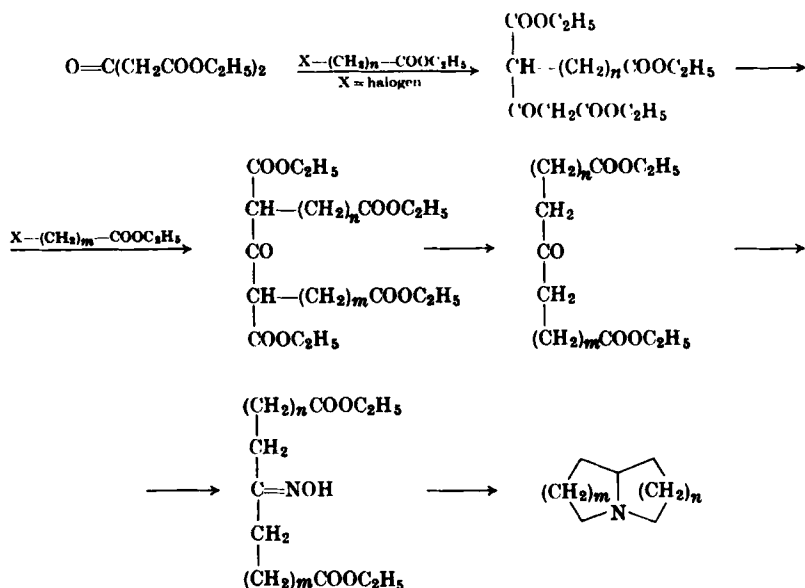
Conversion of ketoesters into various bicyclic amines and related compounds can also be effected according to Scheme 4.⁴³

Leonard and Burk⁴⁴ found that Mannich bases of the pyrrole series are convenient starting compounds for the syntheses of pyrrolizidine

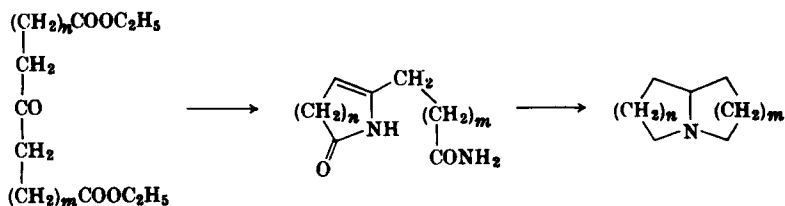
⁴² N. J. Leonard and W. E. Goode, *J. Am. Chem. Soc.* **72**, 5404 (1950).

⁴³ K. Tsuda and S. Saeki, *J. Org. Chem.* **23**, 91 (1958).

⁴⁴ N. J. Leonard and E. H. Burk, *J. Am. Chem. Soc.* **72**, 2543 (1950).



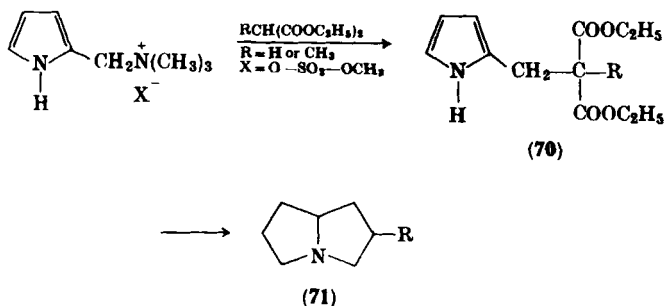
SCHEME 4



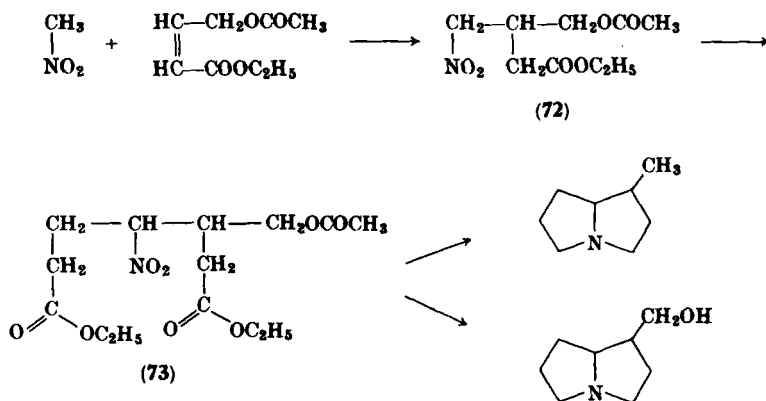
and various 2-substituted pyrrolizidines; quaternary salts of these bases react readily with malonic ester and its derivatives. The condensation products obtained (70) are transformed by reductive cyclization into pyrrolizidine bases (71). Attempted application of the method to the synthesis of 2-phenyl- and 2-amino-pyrrolizidine was unsuccessful.

This method of reductive cyclization is most important for the synthesis of simple pyrrolizidine homologues. It was used also in the synthesis of 1-hydroxymethylpyrrolizidine reported by Leonard and Felley.⁴⁵ Nitromethane when condensed with ethyl γ -acetoxyproton-

⁴⁵ N. J. Leonard and D. Felley, *J. Am. Chem. Soc.* **72**, 2537 (1950).

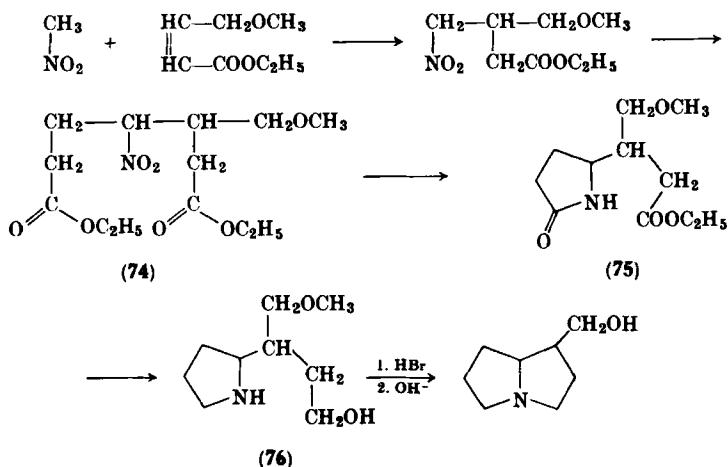


ate afforded the corresponding addition product (72), which was converted into diethyl β -acetoxymethyl- γ -nitropimelate (73) by condensation with ethyl acrylate. Reductive cyclization of 73 resulted in only trace amounts of 1-hydroxymethylpyrrolizidine, which was isolated as its picrate. This was most probably a consequence of the drastic conditions having caused hydrogenolysis of the hydroxymethyl to a methyl group. Less drastic conditions resulted in a negligible yield of the product formed by reductive cyclization.



Ježo and Kalač⁴⁶ have developed another, more efficient, route to 1-hydroxymethylpyrrolizidine. A two-step Michael condensation of nitromethane with ethylmethoxycrotonate and then with ethyl acrylate resulted in ethyl β -methoxymethyl- γ -nitropimelate (74). The latter yields 2-(2-carboethoxy-1-methoxymethylethyl)pyrrolid-5-one (75) on hydrogenation over Raney nickel and 2-(3-hydroxy-1-

⁴⁶ J. Ježo and V. Kalač, *Chem. Zvesti* 11, 696 (1957); *Chem. Abstr.* 52, 10052g (1958).



methoxymethylpropyl)pyrrolidine (76) on subsequent reduction with lithium aluminum hydride. Compound 76, when treated with hydrobromic acid, afforded 2-(3-bromo-1-hydroxymethylpropyl)pyrrolidine which was converted without isolation into 1-hydroxymethylpyrrolizidine. The amino-alcohol obtained appeared to be a mixture of two racemates with (+)-isoretronecanol predominating.

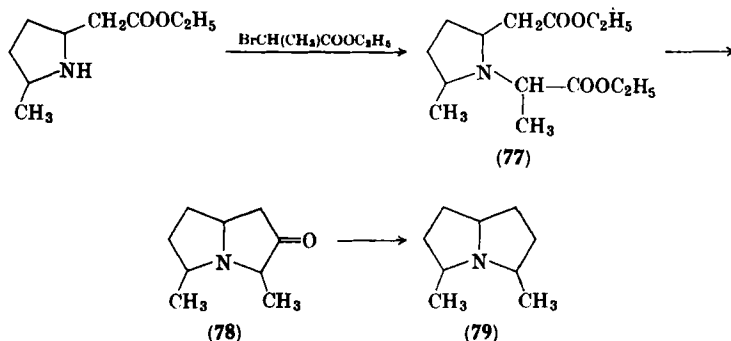
E. DIECKMANN CONDENSATION OF PYRROLIDINE DERIVATIVES

This synthetic route is based on ring closure by Dieckmann condensation of 1,2-bis-carbalkoxyalkylpyrrolidines. It has gained special importance during the last few years, after application to several total syntheses of naturally occurring pyrrolizidine bases. The usual starting compounds employed in this route are esters of α -pyrrolidineacetic acid, proline, and their homologues, which are converted into *N*-substituted dialkyl dicarboxylates. The esters of the dicarboxylic acids are subjected to Dieckmann condensation and subsequent ketonic hydrolysis; the resultant ketones are used in further reactions.

The method was originally proposed by Clemo and Metcalfe⁴⁷ for the preparation of 3,5-dimethylpyrrolizidine. Condensation of ethyl (5-methyl-2-pyrrolidyl)acetate with ethyl α -bromopropionate resulted in the corresponding dicarboxylate (77), which was converted by cyclization and subsequent hydrolysis and decarboxylation into 3,5-

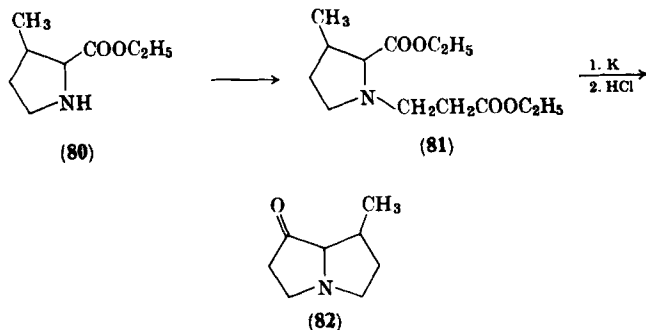
⁴⁷ G. R. Clemo and T. P. Metcalfe, *J. Chem. Soc.* 606 (1936).

dimethyl-2-pyrrolizidone (78). Wolff-Kishner reduction of this compound led to 3,5-dimethylpyrrolizidine (79). Similarly, Clemo and Melrose⁴⁸ have synthesized pyrrolizid-2-one and converted it into



2-methylpyrrolizidine by the action of methylmagnesium bromide, followed by dehydration of the resultant hydroxy compound and hydrogenation.

The synthesis of 1-methylpyrrolizid-7-one⁴⁹ was very important for final confirmation of the structure of the naturally occurring pyrrolizidine bases. The starting ethyl ester of 3-methylproline (80), obtained by analogy with proline,⁵⁰ was condensed with ethyl acrylate and the condensation product (81) converted into 1-methylpyrrolizidine-7-one (82) by cyclization and ketonic hydrolysis. A similar route starting with the ethyl ester of 3-methyl-L-proline afforded optically active



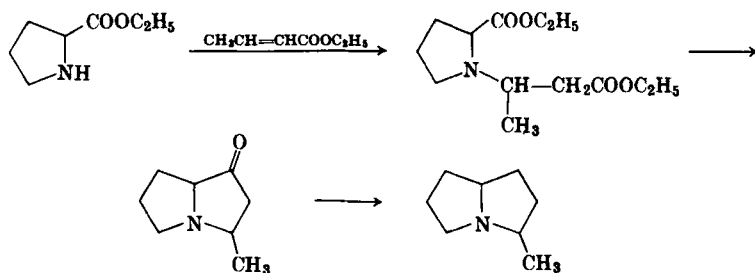
⁴⁸ G. R. Clemo and T. Melrose, *J. Chem. Soc.* 424 (1942).

⁴⁹ R. Adams and N. J. Leonard, *J. Am. Chem. Soc.* 66, 257 (1944).

⁵⁰ E. Fischer and G. Zemplén, *Ber.* 42, 2989 (1909).

1-methylpyrrolizid-7-one. The compound was identical to (-)-retronecanone, which is obtained upon degradation of a number of alkaloids.

The method was also applied to the synthesis of 3-methylpyrrolizidine via 3-methylpyrrolizid-1-one⁵¹ (see Scheme 5).



SCHEME 5

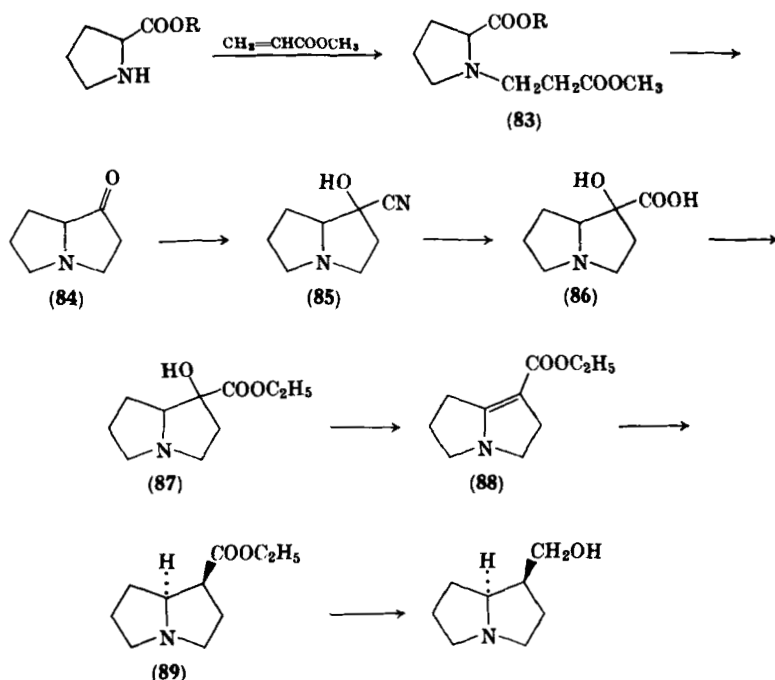
As already mentioned, this route has been especially important for the preparation of naturally occurring pyrrolizidine bases. Recently, it afforded synthetic 1-hydroxymethylpyrrolizidine, 1-hydroxymethyl-7-hydroxypyrrolizidine, and 1-hydroxymethyl-7-hydroxy-1,2-dehydropyrrolizidine (retronecine).

The first stereospecific synthesis of (±)-isoretronecanol was accomplished by Kochetkov *et al.*^{52, 53} who effected ring closure by Dieckmann condensations. Condensation of the ethyl esters of proline with methyl acrylate afforded methyl β-(N-2-carboethoxypyrrolidine)propanoate (**83**). The latter was converted into pyrrolizid-1-one (**84**) by Dieckmann condensation followed by ketonic cleavage of the ketoester. Reaction of pyrrolizid-1-one (**84**) with acetone cyanohydrin gave 1-hydroxy-1-cyanopyrrolizidine (**85**), which was hydrolyzed to give 1-hydroxypyrrolizidine-1-carboxylic acid (**86**); **86** was isolated as the hydrochloride or as the ethyl ester (**87**). Dehydration of the hydroxyester (**87**) might yield the unsaturated ester **88** or its isomer, with the double bond between C-1 and C-2, as well as a mixture of these compounds. The structure of the unsaturated ester was proved by reduc-

⁵¹ N. J. Leonard, F. E. Fischer, E. Barthel, J. Figueras, and W. C. Wildman, *J. Am. Chem. Soc.* **73**, 2371 (1951).

⁵² N. K. Kochetkov and A. M. Likhosherstov, *Zh. Vses. Khim. Obshchestva im. D. I. Mendeleeva* **5**, 477 (1960); *Chem. Abstr.* **55**, 1574 (1961).

⁵³ N. K. Kochetkov, A. M. Likhosherstov, and A. S. Lebedeva, *Zh. Obshch. Khim.* **31**, 3461 (1961); *Chem. Abstr.* **57**, 3490e (1962).



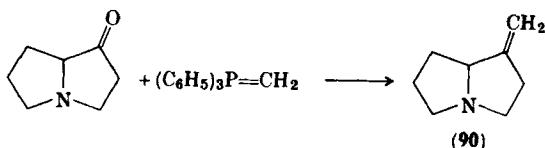
tion with lithium aluminum hydride: the unsaturated alcohol obtained behaved like an enamine and exhibited properties completely different from those of the naturally occurring amino-alcohol, supinidine.⁵⁴ Hence, the dehydration product, or, at least, the major product of this reaction, could be formulated as **88**. The unsaturated ester (**88**) was hydrogenated stereospecifically in the presence of platinum at 7 atm (cf. ref. 55). Since the two rings of the condensed pyrrolizidine system form a dihedral angle with the axis formed by the C—N bond (see Section III,1), hydrogenation proceeds from the sterically unhindered side to give the heliotridane system. The ethyl (\pm)-isoretronecanolate (**89**) obtained was reduced with lithium aluminum hydride to give (\pm)-isoretronecanol.

One of the intermediate compounds of this synthesis was used as starting compound in the total synthesis of one of the "non-ester"

⁵⁴ G. P. Menshikov and E. P. Gurevich, *Zh. Obshch. Khim.* **19**, 1382 (1949); *Chem. Abstr.* **44**, 3486b (1950).

⁵⁵ S. Hünig and H. Kahanek, *Chem. Ber.* **86**, 518 (1953).

alkaloids,^{56, 57} the recently discovered 1-methylenepyrrolizidine.⁵⁸ Pyrrolizid-1-one was condensed with methylenetriphenylphosphorane (cf. ref. 59) and the racemic methylenepyrrolizidine (**90**) obtained resolved with (+)-tartaric acid into the optical antipodes. The levorotatory base had the specific rotations $[\alpha]_D^{28} - 56^\circ$ (pure liquid) and -45.9° (in ethanol); other properties were essentially identical with those of the naturally occurring 1-methylenepyrrolizidine isolated by Culvenor and Smith.⁵⁸ However, it was demonstrated later⁶⁰ that the



base with $[\alpha]_D^{28} - 43.10^\circ$ is actually a partially racemized form which can be additionally resolved with 3-bromocamphor-3-sulfonic acid to give the optically pure material with $[\alpha]_D^{18} - 100^\circ$ (in ethanol).

An interesting stereospecific synthesis of (\pm)-isoretronecanol was proposed more recently by Adams *et al.*^{61, 62} The synthesis is based on closure of the pyrrolizidine ring by a reaction involving simultaneous ester condensation and *N*-acylation. Condensation of ethyl 2-pyrrolidylacetate (**91**) with diethyl oxalate (cf. refs. 63 and 64) in the presence of sodium ethoxide results in a high yield of 1-carbethoxypyrrolizid-2,3-dione (**92**). The latter can be hydrogenated over rhodium on alumina to give 1-carbethoxy-2-hydroxypyrrolizid-3-one (**93**). Dehydration of **93** with *p*-toluenesulfonyl chloride in pyridine proceeds readily to give 1-carbethoxypyrrolizid-1(8)-en-3-one (**94**), which affords 1-carbethoxypyrrolizid-3-one (**95**) on hydrogenation in the presence of rhodium on alumina under atmospheric pressure at 25° . This hydrogenation was also stereospecific and resulted in the forma-

⁵⁶ N. K. Kochetkov, A. M. Likhosherstov, and A. M. Kritzyn, *Tetrahedron Letters*, No. 3, 92 (1961).

⁵⁷ A. M. Likhosherstov, A. M. Kritzyn, and N. K. Kochetkov, *Zh. Obshch. Khim.* **32**, 2377 (1962); *Chem. Abstr.* **58**, 9154c (1963).

⁵⁸ C. C. J. Culvenor and L. W. Smith, *Australian J. Chem.* **12**, 255 (1959).

⁵⁹ G. Wittig, H. Eggers, and P. Duffner, *Ann. Chem.* **619**, 10 (1958).

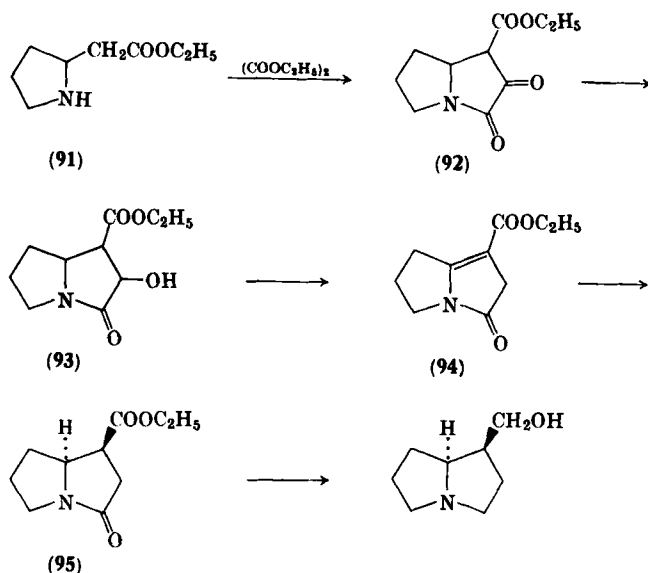
⁶⁰ C. C. J. Culvenor and L. W. Smith, *Australian J. Chem.* **15**, 328 (1962).

⁶¹ M. D. Nair and R. Adams, *J. Org. Chem.* **26**, 3059 (1961).

⁶² R. Adams, S. Mijano, and M. D. Nair, *J. Am. Chem. Soc.* **83**, 3323 (1961).

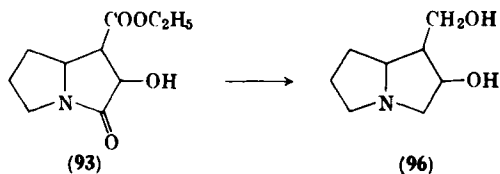
⁶³ P. L. Southwick and L. L. Seivard, *J. Am. Chem. Soc.* **71**, 2532 (1949).

⁶⁴ P. L. Southwick and R. T. Crouch, *J. Am. Chem. Soc.* **75**, 3414 (1953).



tion of the heliotridane system (cf. refs. 65 and 66). Reduction of **95** with lithium aluminum hydride in tetrahydrofuran leads to (\pm)-isoretronecanol. The authors erroneously^{61, 62} claimed the unsaturated ester **94** to be 1-carbethoxypyrrolizid-1(2)-en-3-one. As demonstrated later,⁶⁷ the correct structure must be formulated as **94**, which explains their failure to reduce the compound to supinidine.

To confirm the structures of a number of naturally occurring pyrrolizidine amino-alcohols, **93** was reduced with lithium aluminum hydride to 1-hydroxymethyl-2-hydroxypyrrolizidine (**96**). The compound



would not give a cyclic sulfite ester under the conventional conditions, and this fact seems to favor a *trans* configuration at C-1 and C-2. The

⁶⁵ R. Adams and E. F. Rogers, *J. Am. Chem. Soc.* **63**, 537 (1941).

⁶⁶ R. Adams and J. E. Mahan, *J. Am. Chem. Soc.* **65**, 2009 (1943).

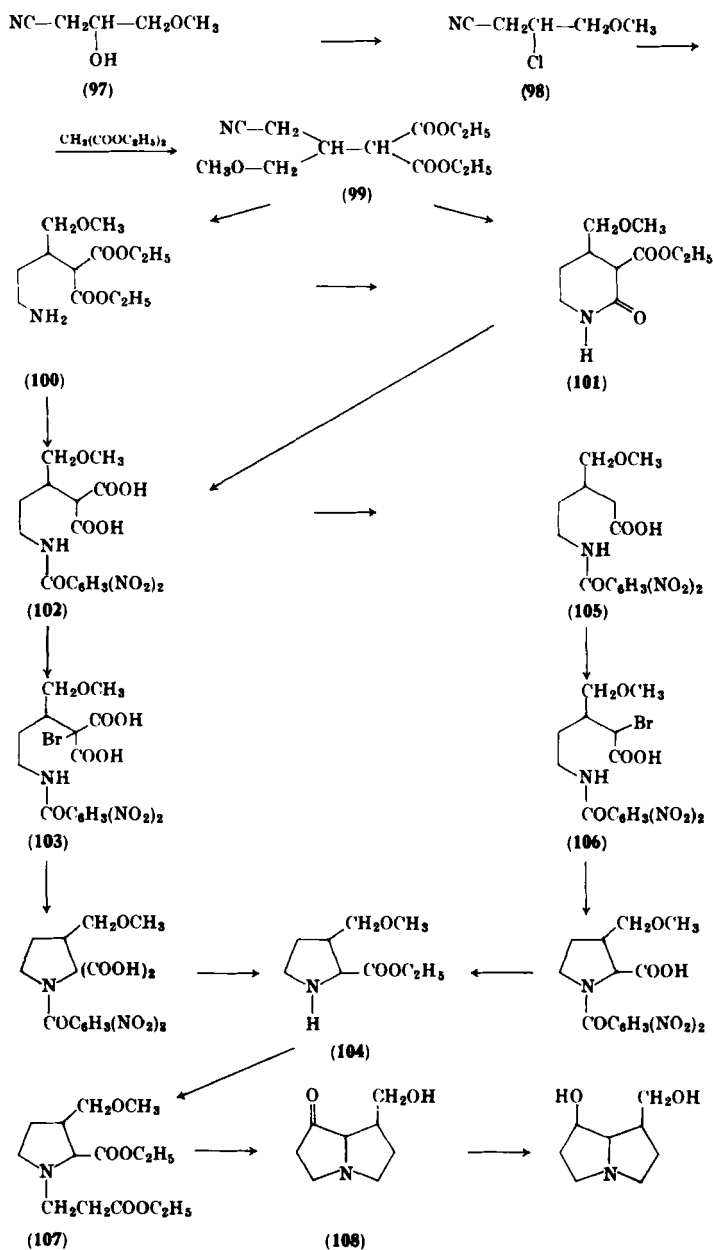
⁶⁷ B. M. Goldschmidt, *J. Org. Chem.* **27**, 4057 (1962).

substance (96) obtained proved not to be identical with naturally occurring macronecine, but the possibility exists that it is a racemic form of hastanecine or of turneforcidine.

It appeared a considerably more difficult problem to synthesize the naturally occurring dihydric pyrrolizidine alcohols. This was achieved only very recently. The first synthesis of 1-hydroxymethyl-7-oxypyrrolizidine, identical with naturally occurring platynecine, was achieved by Ježo *et al.*⁶⁸ as outlined in Scheme 6. 3-Chloro-4-methoxybutyronitrile (98), obtained by reacting 2-hydroxy-3-methoxybutyronitrile (97) with thionyl chloride, was condensed with sodium malonate to give 1-methoxy-3-cyano-*iso*-propylmalonate (99), which could be converted into either ethyl 5-amino-3-methoxymethyl-2-carboethoxyvalerate (100) (hydrogenation at 120 atm at 25° over platinum) or 4-methoxymethyl-3-carboethoxy-2-piperidone (101) (hydrogenation at 120–150° and 80 atm over Raney nickel). Compounds 100 and 101 yielded 5-(3',5'-dinitrobenzamido)-3-methoxymethyl-2-carboxyvaleric acid (102) on alkaline hydrolysis followed by acylation with 3,5-dinitrobenzoyl chloride. The acid could be converted into ethyl 3-methoxymethylpyrrolidine-2-carboxylate by either of two alternative methods: (a) Bromination in glacial acetic acid, cyclization of the bromo-acid (103) to the corresponding pyrrolidine-dicarboxylic acid, and subsequent hydrolysis with hydrochloric acid, followed by decarboxylation, to yield the pyrrolidine-carboxylic acid, which was isolated as its ethyl ester (104). (b) Decarboxylation of 102 to give 5-(3',5'-dinitrobenzamido)-3-methoxymethylvaleric acid (105), bromination of the latter to give 5-(3',5'-dinitrobenzamido)-3-methoxymethyl-2-bromovaleric acid (106), and subsequent cyclization of this in the presence of alkali to yield 1-(3',5'-dinitrobenzoyl)-3-methoxymethylpyrrolidine-2-carboxylic acid. The latter was transformed by acid hydrolysis and esterification into ethyl 3-methoxymethylpyrrolidine-2-carboxylate (104). This key intermediate (104) yielded the corresponding addition product (107) on refluxing with ethyl acrylate. 1-Hydroxymethyl-7-oxopyrrolizidine (108) was obtained from 107 by Dieckmann condensation in the presence of potassium and subsequent acid hydrolysis of the ketoester.

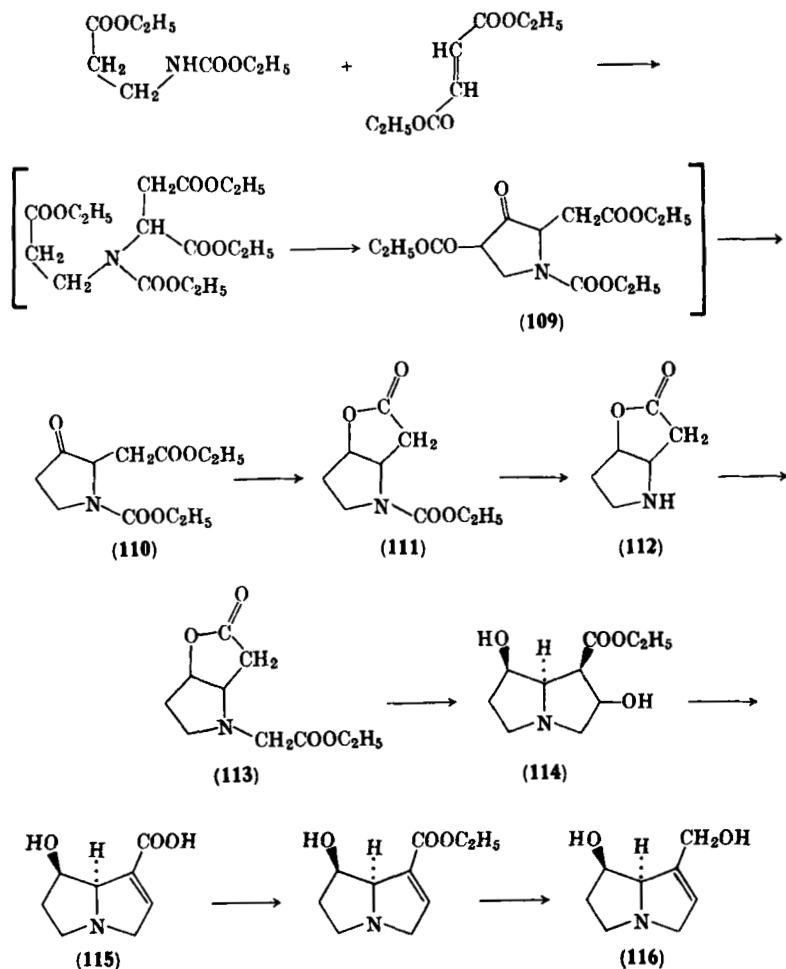
The final product, 1-hydroxymethyl-7-hydroxypyrrolizidine (stereochemistry unknown), was obtained from 108 by hydrogenation in the presence of platinum.

⁶⁸ K. Babor, J. Ježo, V. Kalač, M. Karvaš, and K. Tihlárík, *Chem. Zvesti* **14**, 679 (1960); *Chem. Abstr.* **55**, 17620a (1961).



SCHEME 6

The most outstanding achievement of synthetic pyrrolizidine chemistry is the recently published⁶⁹ total stereospecific synthesis of (+)-retronecine, a constituent of many alkaloids (see Scheme 7).



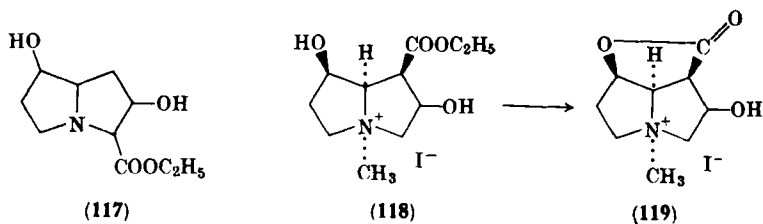
SCHEME 7

The starting ethyl *N*-carbethoxypyrrolid-3-one-2-acetate (110) was obtained by a previously described method⁷⁰ which is based on con-

⁶⁹ J. A. Geissman and A. C. Waiss, *J. Org. Chem.* **27**, 139 (1962).

⁷⁰ J. W. Clark-Lewis and P. J. Mortimer, *J. Chem. Soc.* 189 (1961).

densation of *N*-carbethoxy- β -aminopropionate with fumarate in the presence of sodium followed by saponification, decarboxylation, and esterification of the resulting ketoester. Platinum-catalyzed reduction of **110** afforded hydroxypyrrolidine, which was transformed without isolation, into lactone **111**. Reduction of **110** with sodium borohydride led to a mixture of lactone **111** and the corresponding hydroxyester (most probably with the carbethoxy and hydroxy groups in the *trans*-position). Lactone **112**, obtained by hydrolysis and subsequent lactonization of **111**, was alkylated with ethyl bromoacetate, and the *N*-carbethoxymethyl-lactone **113** subjected to cyclization in the presence of potassium ethylate in benzene. The product of this reaction was hydrogenated over platinum to give the hydroxyester **114**. Had Dieckmann cyclization proceeded in the other possible direction, one would expect the hydroxyester **114** to have structure **117**. To establish its structure, **114** was converted into the corresponding methiodide (**118**), which readily yielded lactone **119**. This ready lactonization,

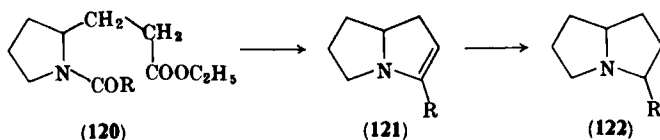


together with the IR spectrum of the lactone, indicated that it had a five-membered ring, providing evidence in favor of structure **114** and against **117**. On the other hand, the readiness of lactonization reveals the *cis*-relationship of the carbethoxy and hydroxy groups at C-1 and C-7. These facts suggest a retronecine-like, i.e. *trans*, configuration of the hydroxyl group at C-7 and the hydrogen at C-8 in the hydroxyester **114**. Treatment of **114** with barium hydroxide resulted, in addition to hydrolysis of the ester grouping, in dehydration to yield the unsaturated acid **115**. The ethyl ester of **115** was reduced to the final product, (±)-retronecine (**116**). Racemic retronecine was resolved into optical antipodes using (+)-camphoric acid. The (+)-retronecine base was identical with the naturally occurring compound.

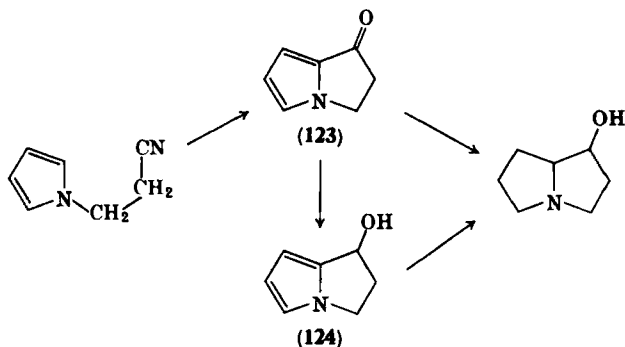
Rapid advances in the synthesis of naturally occurring pyrrolizidine bases can be expected, and the most promising method for this purpose is the Dieckmann cyclization of pyrrolidine derivatives.

F. OTHER METHODS

A few published pyrrolizidine syntheses cannot be classified under any of the above headings. An interesting synthesis of 3-substituted pyrrolizidines was described by Murakoshi.⁷¹ *N*-Acyl derivatives of ethyl (α -pyrrolidine)- β -propionate can be converted by distillation over soda-lime into 3-substituted 2,3-dehydropyrrolizidines (121), which afford 3-substituted pyrrolizidines (122) on catalytic hydrogenation.



A method for the preparation of 1-hydroxypyrrolizidine was published by Adams *et al.*⁷² Cyclization of 1-(β -cyanoethyl)pyrrole under the conditions of the Houben-Hoesch reaction gave rise to 1-oxo-3*H*-1,2-dihydropyrrolo(1,2-*a*)pyrrole (123) (cf. refs. 48 and 73), which can be converted into 1-hydroxypyrrolizidine by either direct hydrogenation over rhodium on alumina or hydrogenation of the corresponding hydroxy derivative 124. This route has some interest as a potential



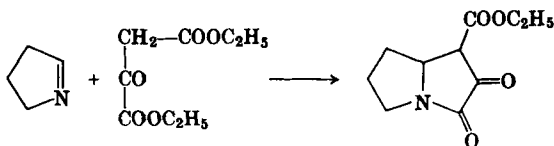
method for the preparation of other functionally substituted pyrrolizidine derivatives.

⁷¹ J. Murakoshi, *Yakugaku Zasshi* **78**, 598 (1958); *Chem. Abstr.* **52**, 18409f (1958).

⁷² R. Adams, S. Mijano, and D. Fleš, *J. Am. Chem. Soc.* **82**, 1466 (1960).

⁷³ G. R. Clemo and G. R. Ramage, *J. Chem. Soc.* **49** (1931).

The synthesis of 1-carbethoxy-2,3-dioxopyrrolizidine (cf. refs. 61 and 62) starting with Δ^1 -pyrroline and ethyl oxalacetate has been reported.⁶⁷



The synthesis of pyrrolizidine derivatives by condensation of di-(4-oxo-*n*-butyl)amine is considered in Section V in conjunction with the biogenesis of naturally occurring pyrrolizidines.

III. Stereochemistry of Pyrrolizidine Bases

Pyrrolizidine derivatives with at least one substituent, and particularly the pyrrolizidine alkaloid components, have one or more asymmetric carbon atoms. The stereochemistry of pyrrolizidine was clarified for the most part in the course of investigation of the naturally occurring pyrrolizidine alcohols. Here, the problems of relative and absolute configuration and of stereoisomeric transformations will be considered.

A. RELATIVE CONFIGURATION OF PYRROLIZIDINE BASES

It is well known that *trans*-bicyclo[3,3,0]octane is a rigid and strained system, whereas the *cis*-isomer is almost strain-free. Pyrrolizidine differs in that one of the carbon atoms is substituted by a trivalent nitrogen atom which does not rigidly fix the bicyclic system. For this reason, pyrrolizidine, although it probably occurs in the preferred *cis*-conformation,⁷⁴ has no stereoisomers. The two rings of the pyrrolizidine system form a dihedral angle with the axis along the C(8)—N bond.

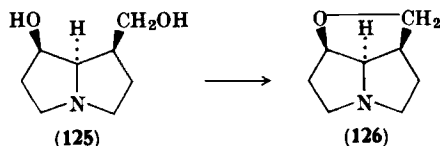
Orekhov and Konovalova^{75, 76} noticed the ready dehydration of platynecine (**125**) to give anhydroplatynecine (**126**) on treatment with phosphorus trichloride, pentachloride, and oxychloride; thionyl

⁷⁴ G. Fodor, *Chem. Ind. (London)* 1424 (1954).

⁷⁵ A. Orekhov and R. Konovalova, *Ber.* **68**, 1886 (1935).

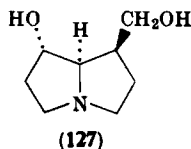
⁷⁶ R. Konovalova and A. Orekhov, *Ber.* **69**, 1908 (1936).

chloride; or sulfuric acid. The authors consider this to be a consequence of the short distance between the two hydroxyl groups enabling the formation of a five- or six-membered ring. On considering a molecular



model of anhydroplatynecine, Leonard and Felley⁴⁵ concluded that the compound can only exist either as **126** or its mirror image, i.e., with the ether bond in the *trans*-position with respect to the hydrogen atom at C-8. This evidence brought no information concerning the configuration of the hydroxyl group at C-7 of platynecine, since there remain possibilities of both retention and inversion of configuration at C-7 during etherification in the presence of the above-mentioned reagents. However, clearly, the configuration at C-1 is retained, so that in platynecine the hydroxymethyl group occupies the *trans*-position with respect to the hydrogen atom at C-8.

Menshikov and Kuzovkov⁷⁷ obtained a platynecine diastereoisomer, dihydroxyheliotridane (**127**), by catalytic hydrogenation of heliotridine. This diastereoisomer appeared to be incapable of forming an anhydro derivative.

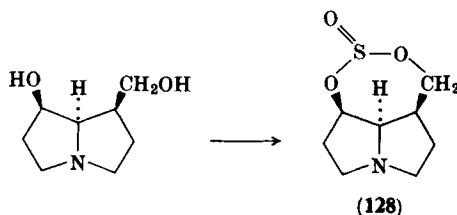


If we assume that the above dehydration occurs with retention of configuration at C-7, the ready formation of the anhydro derivative from platynecine and the inertness of dihydroxyheliotridane apparently indicate a *cis*-relationship of the C-7 hydroxyl group with respect to the hydroxymethyl group in platynecine and a *trans*-conformation in dihydroxyheliotridane.^{1, 78} A reversed relationship would follow from the alternative assumption of inversion at C-7.

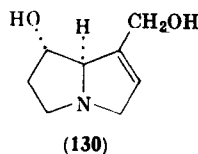
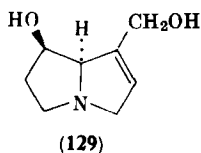
⁷⁷ G. P. Menshikov and A. D. Kuzovkov, *Zh. Obshch. Khim.* **19**, 1702 (1949); *Chem. Abstr.* **44**, 1113g (1950).

⁷⁸ G. P. Menshikov, *Usp. Khim.* **22**, 1138 (1953); *Chem. Abstr.* **48**, 953a (1954).

The position was resolved by Adams and Van Duuren.⁷⁹ Platynecine, when treated with thionyl chloride under mild conditions, yields the cyclic sulfite **128**, whereas no analogous compound can be obtained by similar treatment of dihydroxyheliotridane. The sulfite



(128) is hydrolyzed at 25° with dilute sodium hydroxide to regenerate platynecine. Molecular models of platynecine sulfite indicated the molecule to be relatively strain-free only in the configuration with the sulfite grouping in the *trans*-position with respect to the hydrogen atom at C-8. Hydrolysis of the sulfite with dilute alkali yielded the original platynecine, thus excluding the possibility of inversion during thionyl chloride treatment. Hence, in platynecine the —CH₂OH and —OH groups are in the *cis*-configuration to each other and they are *trans* with respect to the hydrogen atom at C-8. These groups are in the *trans*-configuration in dihydroxyheliotridane. It follows that platynecine is 1-*endo*-hydroxymethyl-7-*endo*-hydroxypyrrolizidine, whereas dihydroxyheliotridane, containing the hydroxymethyl group in the *trans* position with respect to the hydrogen atom at C-8, is 1-*endo*-hydroxymethyl-7-*exo*-hydroxypyrrolizidine. Platynecine and dihydroxyheliotridane are obtained by catalytic reduction of retronecine and heliotridane, which can be thus formulated as **129** and **130**, respectively.

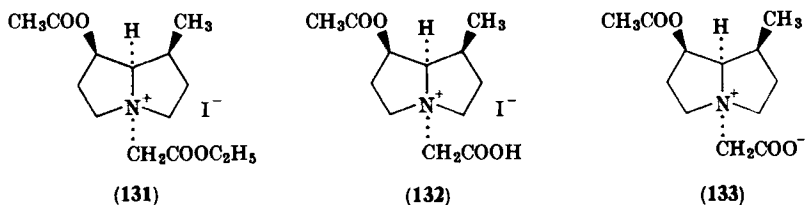


Another approach to elucidation of the configuration at C-7 of pyrrolizidines was outlined by Fodor *et al.*⁸⁰ Retronecanol obtained

⁷⁹ R. Adams and B. L. Van Duuren, *J. Am. Chem. Soc.* **76**, 6379 (1954).

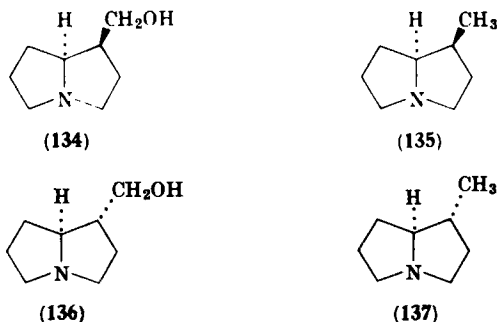
⁸⁰ G. Fodor, I. Sallay, and F. Dutka, *Acta Univ. Szegediensis, Acta Phys. et Chem.* **2**, 80 (1956); *Chem. Abstr.* **51**, 16498f (1957).

from naturally occurring alkaloids was transformed into *N*-carboethoxymethyl-*O*-acetylretronecanolium iodide (**131**), into the corresponding *N*-acetic acid (**132**), and into the betaine (**133**). None of these



compounds was capable of intramolecular lactonization involving re-esterification of the acetoxy group at C-7. This fact suggested the *endo*-configuration of the hydroxyl group in retronecanol and, consequently, in the associated compounds retronecine and platynecine.

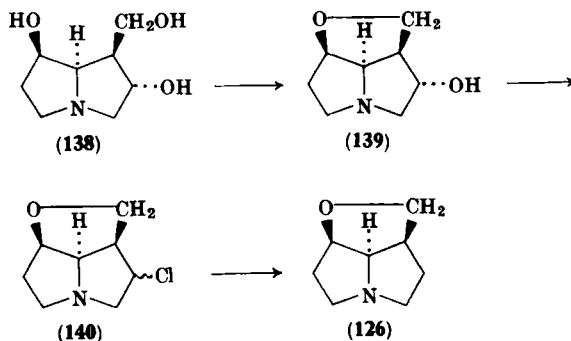
The stereochemistry of the other pyrrolizidine alcohols and related compounds was determined on the basis of comparison of their configurations with those of the above basic compounds.^{2, 45, 81} For example, platynecine can be converted into (–)-isoretronecanol (**134**) under conditions which cannot affect the configuration at C-1, and **134** can then be transformed into (–)-heliotridane (**135**). On the basis of these data, the compounds can be named, respectively, as 1-*endo*-hydroxymethylpyrrolizidine and 1-*endo*-methylpyrrolizidine, and their diastereoisomers (–)-trachelanthamidine (**136**) and (–)-pseudoheliotridane (**137**) as 1-*exo*-hydroxymethylpyrrolizidine and 1-*exo*-methylpyrrolizidine.



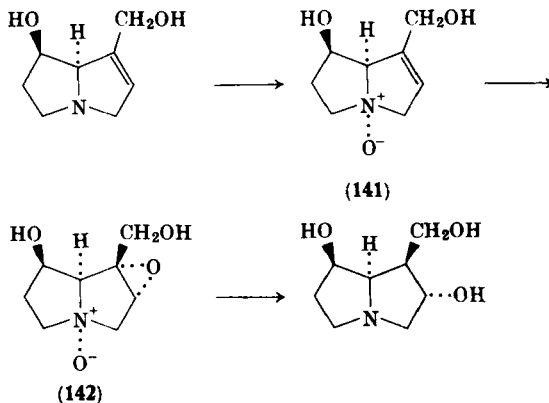
The stereochemistry of rosmarinecine, which contains an additional asymmetric center at C-2, was established by comparison with retro-

⁸¹ R. Adams and K. Hamilt, *J. Am. Chem. Soc.* **64**, 2597 (1942).

necine and platynecine.⁸² Rosmarinecine (**138**) readily yields anhydrososmarinecine (**139**) when treated with concentrated sulfuric acid. The latter can be converted via chloroanhydroplatynecine (**140**) into anhydroplatynecine (**126**); this transformation proves the



configuration at C-1 and at C-7. The configuration at C-2 was decided on the basis of the following synthesis of rosmarinecine. The authors base their argument on the stereospecificity of the oxidation of the double bond of **141** which leaves only the possibility of formation of the oxide in the *exo*-position as shown in **142**. Incidentally, such



stereospecificity is characteristic of hydrogenation of the C(1)—C(2) bond of pyrrolizidine bases; for example, hydrogenation of retro-necine gives platynecine as the sole product.⁶⁵ Hence, the hydroxyl group at C-2 must occupy the *cis*-position with respect to the hydrogen atom at C-8. The orientation of the hydroxyl group at C-2 is confirmed

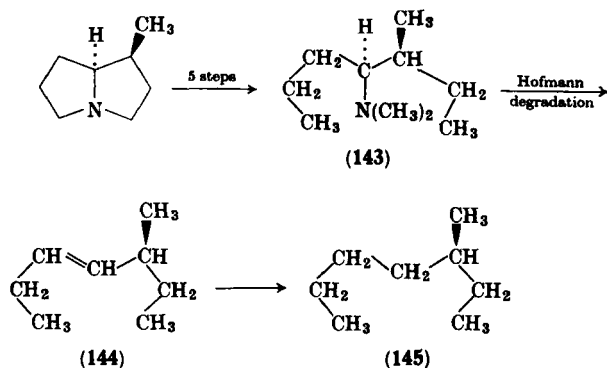
⁸² L. J. Dry, M. J. Koekemoer, and F. L. Warren, *J. Chem. Soc.* 59 (1955).

also by the failure to effect direct dehydration of rosmarinine,⁸³ indicating a *cis*-configuration of the C-1 hydrogen with respect to the C-2 hydroxyl group.

B. ABSOLUTE CONFIGURATION OF PYRROLIZIDINE BASES

The absolute configurations of pyrrolizidine bases were established only very recently. Leonard⁸⁴ attempted to solve the problem by comparing the shifts of molecular rotation of isoretronecanol derivatives with analogous shifts in the lupinine series. However, it was demonstrated later that this approach led to incorrect conclusions.

The absolute configurations of heliotridane and related bases were elucidated originally by Warren and von Klemperer.⁸⁵ Heliotridane was converted, according to Menshikov,^{7, 86} into 4-dimethylamino-3-methylheptane (**143**). On subjection to Hofmann degradation **143** yielded 3-methylhept-4-ene (**144**) as the major product. Catalytic reduction of this compound gave rise to partially racemized (+)-3-methylheptane (**145**), which was assumed to have an *S*-configuration; the same configuration was also assigned on this basis to C-1 of heliotridane.



Another approach to elucidation of the absolute configuration at C-1 was used by Adams and Fleš,⁸⁷ who showed that (–)-3-methyl-5-

⁸³ M. J. Koekemoer and F. L. Warren, *J. Chem. Soc.* 63 (1955).

⁸⁴ N. J. Leonard, *Chem. Ind. (London)* 1455 (1957).

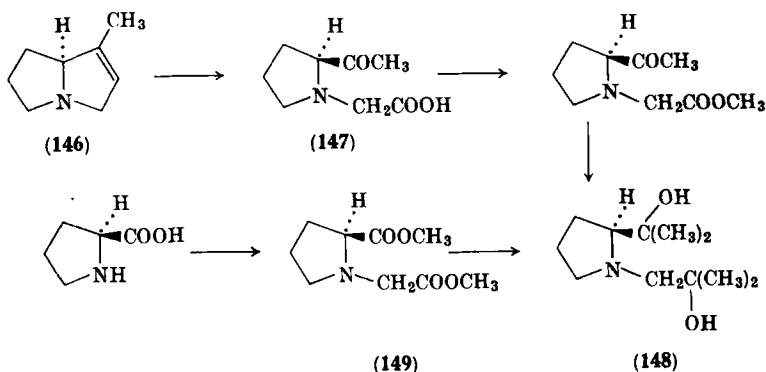
⁸⁵ F. L. Warren and M. E. von Klemperer, *J. Chem. Soc.* 4574 (1958).

⁸⁶ G. Menshikov, *Ber.* 68, 1555 (1935).

⁸⁷ R. Adams and D. Fleš, *J. Am. Chem. Soc.* 81, 4946 (1959).

aminovaleric acid, used earlier as starting compound in the synthesis of (–)-retronecanol,⁴⁹ has the *S*-configuration, thus indicating an *S*-configuration of retronecanol and related bases.

The absolute configuration was also established unequivocally for C-8 of naturally occurring pyrrolizidine bases.⁸⁸ It was demonstrated in the course of the structural analysis of isoheliotridene (146), obtained by degradation of the alkaloid monocrotaline, that ozonolysis of this compound affords 2-acetylpyrrolidine-1-acetic acid (147).⁶⁶ The (–)-methyl ester of this acid was condensed with methylmagnesium iodide to give (–)-1-(2-hydroxy-2-methylpropyl)-2-(1-hydroxy-1-methylethyl)pyrrolidine (148). The same glycol (148) was obtained



from L-(–)-proline by condensing its methyl ester with methyl bromoacetate and subsequent treatment of the methyl (–)-2-carbomethoxy-1-pyrrolidylacetate (149) with excess methylmagnesium iodide. The two compounds were identical, thus confirming the absolute configuration at C-8 of isoheliotridene.

The absolute configurations of the alkaloid 1-methylenepyrrolizidine and related naturally occurring pyrrolizidine bases were also established by stereospecific synthesis.⁸⁹

Pyrrolizid-1-one, obtained from the ethyl ester of L-proline (see Section II, E), was condensed with methylenetriphenylphosphorane to give 1-methylenepyrrolizidine, $[\alpha]_D^{28} - 33^\circ$, the IR spectrum of the latter compound was identical with that of the naturally occurring alkaloid. Notwithstanding the partial racemization of the base during

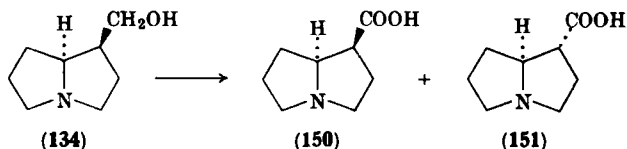
⁸⁸ R. Adams and D. Fleš, *J. Am. Chem. Soc.* **81**, 5803 (1959).

⁸⁹ A. M. Likhoshervostov, A. M. Kritzyn, and N. K. Kochetkov, *Dokl. Akad. Nauk SSSR* **141**, 361 (1961); *Chem. Abstr.* **56**, 11629f (1962).

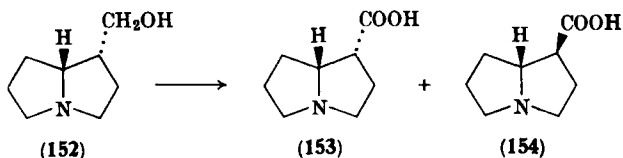
the synthesis (see Section II, E), it exhibited a rotation of the same sign as that of the natural compound. Hence, the latter could be assumed to have the absolute configuration of L-proline and can be named as (8*S*)-1-methylenepyrrolizidine, in complete agreement with the data of Culvenor and Smith.⁵⁸

C. STEREOCHEMICAL TRANSFORMATIONS OF PYRROLIZIDINE DERIVATIVES

Conformational analysis of heliotridane and pseudoheliotridane derivatives reveals the latter to possess the greater stability. This conclusion is confirmed by the predominance of the pseudoheliotridane structures among the products of pyrrolizidine ring closures. The extensive epimerization during oxidation of heliotridane alcohols (cf. ref. 81 and 91) with chromic acid observed by Labensky, Serova, and Menshikov^{78, 90} can be regarded as additional confirmation. Oxidation of isoretronecanol (**134**) results in a mixture of approximately equal amounts of two levorotatory-diastereoisomeric pyrrolizidine-1-carboxylic acids, (–)-isoretronecanolic (**150**) and (–)-trachelanthamidinic acid (**151**). On the other hand, oxidation of lindelophidine (**152**)



results in a mixture of approximately equal amounts of two dextrorotatory-diastereoisomeric forms, (+)-isoretronecanolic (**153**) and (+)-trachelanthamidinic acid (**154**).



It is significant that analogous transformations do not take place during oxidation of amino-alcohols of the pseudoheliotridane

⁹⁰ A. S. Labensky, N. A. Serova, and G. P. Menshikov, *Dokl. Akad. Nauk SSSR* **88**, 467 (1953); *Chem. Abstr.* **48**, 2721e (1954).

⁹¹ R. Willstätter and E. Fourneau, *Ber.* **35**, 1917 (1902).

series.^{78, 90} Neither the amino-alcohols nor the related amino acids isomerize when heated in sulfuric acid of even higher concentrations and at higher temperatures than those used for oxidation of **152**. However, it has been demonstrated recently⁹² that pyrrolizidine-1-carboxylic acids of the heliotridane series isomerize when heated in concentrated hydrochloric acid at 180–200° this stereoisomeric transformation occurs not only with (\pm)-isoretronecanolic acid, but also with the antipodes. In the latter case, the reaction involves epimerization at C-1 and not at C-8, thus no racemization results.

IV. Reactions of Pyrrolizidine and Its Derivatives

The chemical behavior and reactions of pyrrolizidine derivatives were investigated for the most part during structural analysis of naturally occurring pyrrolizidine alkaloids and in the course of the syntheses of their degradation fragments; there are several publications concerned specially with this subject. Pyrrolizidine derivatives are typical tertiary amines, and consequently their chemical behavior is a combination of the properties of tertiary amines and of those of the substituent functions. However, some peculiarities of the class can be explained only in terms of the configuration of the bicyclic system.

Naturally, 3- and 5-oxopyrrolizidines fall outside the group; they show the properties typical of lactams. This section is concerned with a brief discussion of the following types of reactions of pyrrolizidine derivatives:

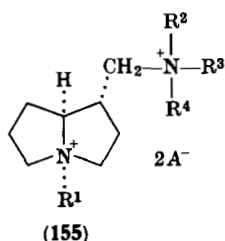
- (A) Reactions at the pyrrolizidine nitrogen atom.
- (B) Reactions of hydroxy-, oxo-, carboxy-, and other substituted pyrrolizidines.
- (C) Reactions of halogenopyrrolizidines.
- (D) Reactions of unsaturated pyrrolizidines.
- (E) Reactions of pyrrolizidines containing amide groups.
- (F) Reactions involving opening the pyrrolizidine ring.

A. REACTIONS AT THE PYRROLIZIDINE NITROGEN ATOM

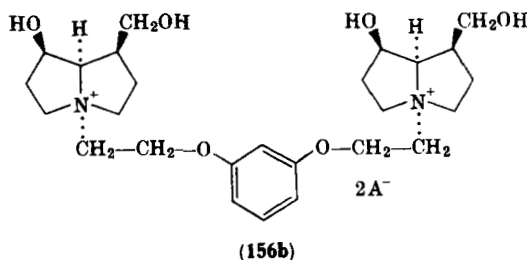
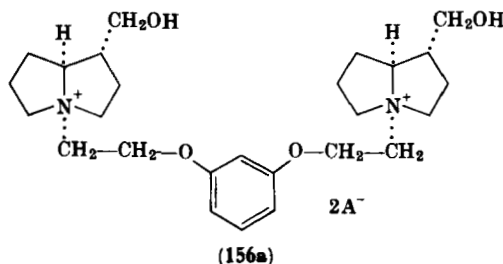
Pyrrolizidines are strong bases. They readily yield salts with a wide variety of organic and inorganic acids; these salts can be used for identification (e.g. methiodides) as well as in a number of syntheses,

⁹² A. M. Likhoshesterov, V. N. Kulakov, and N. K. Kochetkov, *Zh. Obshch. Khim.* **34**, 2798 (1964).

particularly for the preparation of physiologically active agents. A singular example of a quaternary salt is described by Šorm and Beranek,⁹⁰ who have obtained the 1-azoniumtricyclo-[3.3.3.0]-undecane ion (see Section II, C). Quaternary salts of types **155** and **156** were prepared as potential drugs.⁹³ Compounds of type **155** apparently exhibit high ganglion-blocking activity. Quaternary salts of type **156** show high curare-like activity. One of them (**156b**) is now in clinical use under the name "diplacin"⁹⁴ as a substitute for *d*-tubocurarine



- a. $R^1 = R^2 = R^3 = \text{CH}_3$; $R^4 = \text{CH}_2\text{C}_6\text{H}_5$
 b. $R^1 = R^2 = R^3 = \text{CH}_3$; $R^4 = (\text{CH}_2)_7\text{CH}_3$
 c. $R^1 = R^2 = R^3 = R^4 = \text{C}_2\text{H}_5$



⁹³ A. D. Kusovkov, M. D. Mashkovsky, A. V. Danilova, and G. P. Menshikov, *Dokl. Akad. Nauk SSSR* **103**, 251 (1955); *Chem. Abstr.* **50**, 5696a (1956).

⁹⁴ M. D. Mashkovsky and A. I. Briskin, *Klinich. Med.* **30**, No. 10, 74 (1952).

chloride. Considerable curare-like activity is also characteristic of thesine bis-methiodide.^{95, 96} Quaternization has been utilized in a number of syntheses of pyrrolizidine derivatives (see Section II, B)²⁷ and in elucidation of the configuration at C-7 in retronecanol (see Section III, A).⁸⁰

Pyrrolizidine bases readily form *N*-oxides. Many pyrrolizidine alkaloids occur in plants in the form both of the bases and the *N*-oxides; transformation of the tertiary amine into the *N*-oxide is closely related to the vegetation period.⁹⁷⁻⁹⁹ The oxidation, as well as the reverse reaction, can be readily accomplished by chemical methods. For example, the alkaloid trachelanthamine, when treated with hydrogen peroxide, affords the alkaloid trachelanthine (trachelanthamine *N*-oxide), the latter reverting to trachelanthamine when reduced with sulfur dioxide.¹⁰⁰

B. REACTIONS OF HYDROXY-, OXO-, CARBOXY-, AND OTHER SUBSTITUTED PYRROLIZIDINES

The properties and reactions of amino-alcohols, obtained largely by hydrolysis of naturally occurring alkaloids, were investigated primarily for the purposes of structural analysis and the preparation of physiologically active derivatives. Many authors have described acylation of pyrrolizidine alcohols with benzoyl chloride and acetic anhydride (see, e.g., refs. 83 and 101). Trachelanthamidine benzoate and *p*-aminobenzoate were prepared especially for testing of their physiological activity.¹⁰² The *p*-aminobenzoate was obtained by treatment of trachelanthamidine with *p*-nitrobenzoyl chloride and subsequent reduction of the nitro group with iron in 20% acetic acid. The compound exhibited an anesthetic activity close to that of cocaine.

⁹⁵ M. D. Mashkovsky, *Farmakol. i Toksikol.* **6**, No. 1, 25 (1943).

⁹⁶ M. D. Mashkovsky, *Farmakol. i Toksikol.* **18**, No. 6, 3 (1955); *Chem. Abstr.* **50**, 6685d (1956).

⁹⁷ L. Ya. Areshkina, *Dokl. Akad. Nauk SSSR* **61**, 483 (1948).

⁹⁸ L. Ya. Areshkina, *Dokl. Akad. Nauk SSSR* **65**, 711 (1949).

⁹⁹ L. Ya. Areshkina, *Biokhimiya* **22**, 527 (1957); *Chem. Abstr.* **52**, 2180i (1958).

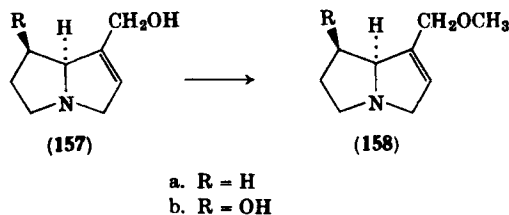
¹⁰⁰ G. P. Menshikov and G. M. Borodina, *Zh. Obshch. Khim.* **15**, 225 (1945); *Chem. Abstr.* **40**, 2141 (1946).

¹⁰¹ G. Menshikov, *Ber.* **66**, 875 (1933).

¹⁰² E. L. Gurevich and G. P. Menshikov, *Zh. Obshch. Khim.* **17**, 1714 (1947); *Chem. Abstr.* **42**, 2598e (1948).

Konovalova and Orekhov¹⁰³ demonstrated that the primary hydroxyl group in platynecine is more reactive to acylation than the secondary. For example, use of more or less drastic conditions yields platynecine di- or mono-benzoate, respectively. Pyrrolizidine alcohols can be esterified with inorganic acids; e.g., mild treatment of platynecine with thionyl chloride yields the cyclic sulfite ester hydrochloride⁷⁹ (see Section III, A).

Pyrrolizidine ethers can be obtained by alkylation. Culvenor and Smith¹⁰⁴ used this reaction in partial synthesis of the recently discovered alkaloids 1-methoxymethyl-1,2-dehydro-8 α -pyrrolizidine (158a) and 7 β -hydroxy-1-methoxymethyl-1,2-dehydro-8 α -pyrrolizidine (158b). The compounds were obtained by alkylating supinidine (157a) or retronecine (157b) with methyl iodide in the presence of



potassium *tert*-butoxide. The same publication described the intramolecular alkylation of 7-hydroxy-1-chloromethyl-1,2-dehydro-8 α -pyrrolizidine to give anhydrotetronecine.

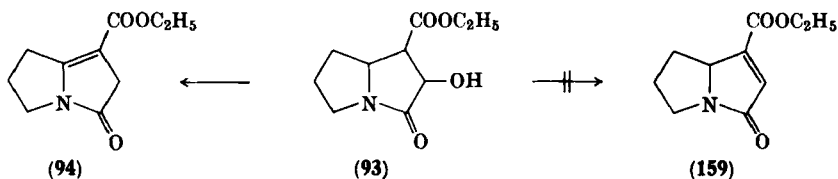
The hydroxy groups of pyrrolizidine amino-alcohols are readily replaced by chlorine atoms upon treatment with thionyl chloride (see, e.g., refs. 101 and 103). In this reaction, the allylic hydroxyl group is more reactive and can be selectively replaced by chlorine.⁷⁹ In some particular cases, methoxyl groups can also be substituted for halogen; e.g., 1 β -methoxymethyl-8 α -pyrrolizidine, when treated with hydrobromic acid, gives rise to the corresponding bromo derivative.¹⁰⁴

Pyrrolizidine alcohols are readily oxidized. Stereoisomeric 1-hydroxymethylpyrrolizidines when oxidized with chromic acid afford stereoisomeric pyrrolizidine-1-carboxylic acids (see Section III, C).^{81,90} Secondary alcohols, when subjected to Oppenauer oxidation or chromic acid treatment, yield amino-ketones (cf. refs. 72, 77, and 81).

¹⁰³ R. A. Konovalova and A. P. Orekhov, *Zh. Obshch. Khim.* **8**, 273 (1938); *Chem. Abstr.* **32**, 5403 (1938).

¹⁰⁴ C. C. J. Culvenor and L. W. Smith, *Australian J. Chem.* **15**, 121 (1962).

Pyrrolizidine amino-alcohols are readily dehydrated; for example, hydroxyheliotridane and retronecanol, when treated with sulfuric acid, afford heliotridene (see e.g., refs. 105 to 107). A more complicated dehydration reaction is the transformation of the alkaloid rosmarinine into the alkaloid senecionine.⁸³ Dehydration of 1-hydroxy-1-carbethoxypyrrolizidine⁵³ in the presence of phosphorus oxychloride in pyridine results mainly in the formation of the $\Delta^{1,8}$ -unsaturated ester (see Section II, E). The authors^{61, 62} claimed that the dehydration product of 1-carbethoxy-2-hydroxy-3-oxopyrrolizidine contained a $\Delta^{1,2}$ -double bond (159). Later, however, the UV, IR, and NMR spectra⁶⁷ revealed that the double bond had migrated: the



reaction in fact yields the unsaturated ester 94. Other types of dehydration lead to the formation of anhydro derivatives. Thus, platynecine^{75, 76} and rosmarinine⁸² are readily dehydrated to give the intramolecular ethers, anhydroplatynecine and anhydrorosmarinine, respectively (see Section III, A).

Only a limited number of pyrrolizidine derivatives with oxo and carboxy substituents have been obtained to date, and these have been prepared mainly during structural analyses of pyrrolizidine bases^{49, 77, 81, 108} or as synthetic intermediates^{53, 61, 69} (see also Section IV, E). 1-Formylpyrrolizidine¹⁰⁹ and 1-hydroxymethyl-7-oxopyrrolizidine⁶⁸ afford 1-hydroxymethylpyrrolizidine and 1-hydroxymethyl-7-hydroxypyrrolizidine, respectively, when hydrogenated in the presence of platinum. Hydrogenation of 2,3-dioxo-1-carbethoxypyrrolizidine in the presence of rhodium on alumina yields 1-carbethoxy-2-hydroxy-3-oxopyrrolizidine.^{61, 62} Wolff-Kishner reduction of 3-methylpyrrolizid-1-one⁵¹ and 3,4-dimethylpyrrolizid-1-one

¹⁰⁵ G. Menshikov, *Ber.* **68**, 1051 (1935).

¹⁰⁶ G. Menshikov and W. Rubinstein, *Ber.* **68**, 2039 (1935).

¹⁰⁷ R. A. Konovalova and A. P. Orekhov, *Zh. Obshch. Khim.* **8**, 391 (1938).

¹⁰⁸ G. P. Menshikov, *Zh. Obshch. Khim.* **16**, 1311 (1946); *Chem. Abstr.* **41**, 3092b (1947).

¹⁰⁹ K. Babor, J. Ježo, V. Kalač, and M. Karvaš, *Chem. Zvesti* **13**, 163 (1959).

results, on the other hand, in the formation of the corresponding deoxy compounds. Pyrrolizid-2-one has been found to react with methylmagnesium iodide.⁴⁸ Pyrrolizid-1-one has been used in a cyanohydrin synthesis^{52, 53} and as starting compound in the synthesis of 1-methylenepyrrolizidine by the Wittig reaction.^{56, 57} Several pyrrolizidine carboxylic acids have been described which carry the carboxyl group in positions 1 and 3. These acids have been esterified,^{20, 24, 53} decarboxylated,¹⁰⁸ and reduced with lithium aluminum hydride to the corresponding alcohols^{20, 21, 30, 53, 61}; their methiodides are also known.⁶⁹

C. REACTIONS OF PYRROLIZIDINE HALIDES

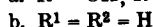
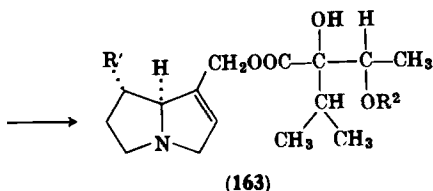
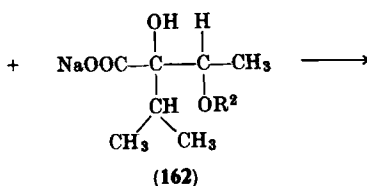
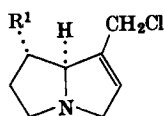
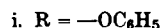
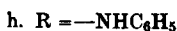
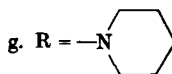
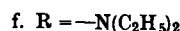
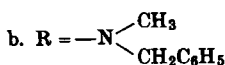
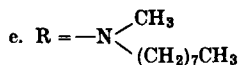
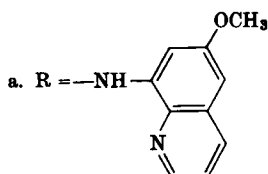
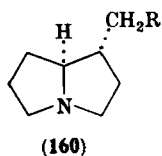
The most general method for preparation of the pyrrolizidine halides is based on substitution of hydroxyl groups of pyrrolizidine alcohols by halogen^{101, 103, 109} and has been widely used for structural elucidation. The allylic chlorine atom of dichloroheliotridine is readily replaced by hydrogen during catalytic hydrogenation over platinum chloride to give 7-chloroheliotridane.¹⁰¹ The chlorine atom at primary and secondary carbon atoms in saturated pyrrolizidine derivatives can be removed by reduction with sodium in alcohol.^{100, 103} Reductive removal of chlorine from a secondary carbon atom and bromine from a primary carbon atom can be affected by hydrogenation over Raney nickel^{81, 104} or with chromous chloride.^{66, 77} In the latter case, the double bond remains unaffected. Galinovsky *et al.*¹¹⁰ have also reduced laburnine tosylate to (+)-pseudoheliotridane with lithium aluminum hydride. Culvenor and Smith¹¹¹ have described an interesting reduction of an allylic chlorine with simultaneous allylic rearrangement; the mono- and di-chloro derivatives of supinidine, heliotridine, and retronecine, when reduced with zinc in sulfuric acid, afford Δ^1 -dehydropyrrolizidine and 1-methylenepyrrolizidine in ratios of 1:3, 1:4, and 1:4, respectively. It is noteworthy that the allylic rearrangement takes place not on substitution of the hydroxyl group by chlorine, but during the subsequent reduction.

Pyrrolizidine halides have been used as starting compounds for the synthesis of physiologically active agents, such as 6-methoxy-8-(pseudoheliotridyl)aminoquinoline (160a)¹⁰² and various other ter-

¹¹⁰ F. Galinovsky, O. Vogl, and H. Nesvadba, *Monatsh. Chem.* **85**, 913 (1954).

¹¹¹ C. C. J. Culvenor and L. W. Smith, *Australian J. Chem.* **14**, 284 (1961).

tiary amines of the pseudoheliotridane series (e.g. **160b–160h**).¹¹² Compound **160a** is an antimalarial agent, but its activity was somewhat less than that of plasmoquine. Quaternary salts of the above amines were also obtained. The corresponding phenyl ether (**160i**)



¹¹² A. D. Kusovkov and G. P. Menshikov, *Zh. Obshch. Khim.* **21**, 2245 (1951); *Chem. Abstr.* **46**, 8130a (1952).

was obtained from 9 chloropseudoheliotridane and potassium phenolate; Culvenor, Dann, and Smith¹¹³ used halogenated derivatives in their partial synthesis of heliotrine and supinine from the corresponding naturally occurring amino-alcohols and necic acids. The primary hydroxyl group was substituted by a chlorine atom, and the resultant chloro compounds (161) condensed with sodium heliotrinatate (162a) or trachelanthate (162b). The reaction resulted in small yields of heliotrine (163a) and supinine (163b). The major side-reaction was polymerization of the chloro derivatives (161) to give quaternary salts.

D. REACTIONS OF UNSATURATED COMPOUNDS OF THE PYRROLIZIDINE SERIES

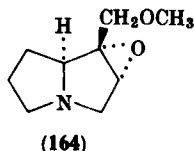
Only pyrrolizidines with one double bond in the ring are considered in the present review. Pyrrolizidine derivatives with a double bond between positions 2-3, 1-8, and 1-2, as well as those with a semicyclic double bond, have been described. However, only the last two types have been identified among the naturally occurring compounds. Unsaturated compounds are readily dehydrogenated catalytically (see, e.g. refs. 48, 58, and 105). This reduction is sometimes accompanied by hydrogenolysis of the allylic hydroxyl group, etc. For example, hydrogenation of retronecine⁶⁵ or heliotridine⁷⁷ with Raney nickel appeared to afford compounds with reduced double bonds as the only products, whereas analogous treatment of both of these compounds and their esters in the presence of platinum leads firstly to hydrogenolysis of the primary hydroxyl group and subsequently to reduction of the double bond (see, e.g., refs. 66, 105, and 114). No elimination of the methoxyl group occurs during hydrogenation of compounds with the group in the 1-position.¹⁰⁴ Hydrogenation always proceeds stereospecifically to give compounds with a *cis*-orientation of the hydrogen atoms at C-1 and at C-8. This is also the case with 1-carbethoxy-1(8)-dehydropyrrolizidine⁵³ (platinum catalyst) and with 1-carbethoxy-3-oxo-1(8)-dehydropyrrolizidine (rhodium on alumina)⁶¹ (cf. ref. 67).

Among other reactions, the synthesis of the epoxide-*N*-oxide from retronecine should be mentioned⁸²; the epoxide yields rosmarinine on hydrogenation over Raney nickel (see Section III, A). The epoxy group has been recently demonstrated to be a constituent of certain

¹¹³ C. C. J. Culvenor, A. T. Dann, and L. W. Smith, *Chem. Ind. (London)* 20 (1959).

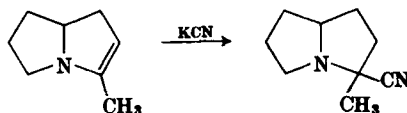
¹¹⁴ G. Barger, T. R. Seshadry, H. E. Watt, and T. Jabuta, *J. Chem. Soc.* 11 (1935).

naturally occurring alkaloids; one of these has structure **164**.¹¹⁵ Attempted synthesis of this compound by oxidation of 1-methoxymethyl-1,2-dehydropyrrolizidine was unsuccessful.



Ozonolysis of isoheliotridene (**146**) afforded a pyrrolidine derivative.⁶⁶ Analogous treatment of 1-methylenepyrrolizidine gave rise to pyrrolizid-1-one.⁵⁸

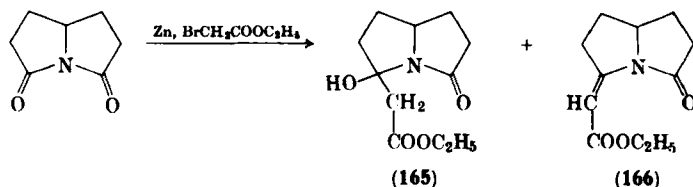
The double bond in the 2,3-position is of the enamine type and is capable of cyanide addition⁷¹:



E. REACTIONS OF PYRROLIZIDINES CONTAINING AN AMIDE GROUP

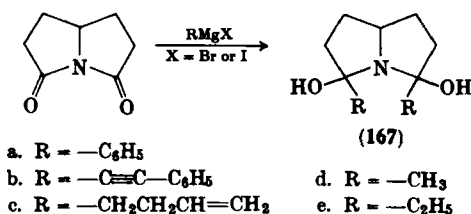
3-Oxo- and 3,5-dioxo-pyrrolizidines can be regarded as mono- and di-lactams, respectively, and hence exhibit typical amide properties. They are readily reduced to amines electrochemically (see, e.g. refs. 29 and 31) or with lithium aluminum hydride (see, e.g., refs. 30 and 33).

3,5-Dioxopyrrolizidine was widely used by Micheel *et al.*^{33, 116} as starting compound in the syntheses of some pyrrolizidine derivatives. Its reaction with phosphorus pentasulfide gave rise to pyrrolizidine-3,5-dithione, and it was converted via a Reformatsky reaction into ethyl 3-oxo-5-hydroxypyrrolizidine-5-acetate (**165**) and ethyl 3-oxo-pyrrolizylidene-5-acetate (**166**). Condensation with organomagnesium

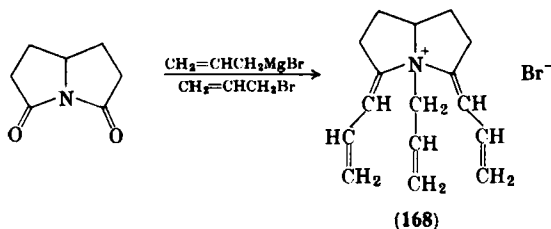


¹¹⁵ C. C. J. Culvenor, J. D. Morrison, A. J. C. Nicholson, and L. W. Smith, *Australian J. Chem.* **16**, 131 (1963).

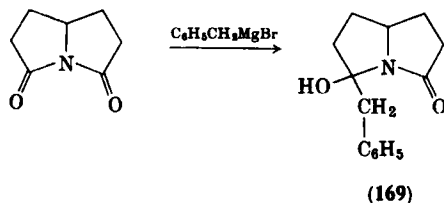
¹¹⁶ F. Micheel and W. Flitsch, *Chem. Ber.* **94**, 1749 (1961).



compounds afforded derivatives of 3,5-dihydroxypyrrolizidine (167). 3,5-Dioxopyrrolizidine gave a product formulated as *N*-allyl-3,5-diallylidene-pyrrolizidinium bromide (168) on treatment with allylmag-



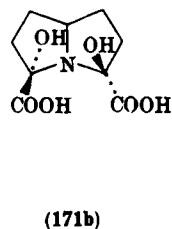
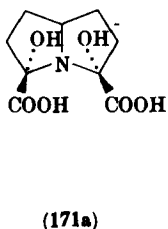
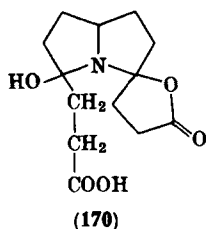
nesium bromide (containing allyl bromide). The same compound reacted with benzylmagnesium bromide to give 3-oxo-5-hydroxy-5-benzylpyrrolizidine (169).



Ozonolysis of 3,5-dihydroxy-3,5-di-(*n*-buten-3-yl)pyrrolizidine (167c) resulted in the formation of pyrrolizidine-3,5-dihydroxy-3,5-bis(3'-propionic acid) monolactone (170). Similar treatment of 3,5-dihydroxy-3,5-bis(phenylethynyl)pyrrolizidine (167b) afforded stereoisomeric 3,5-dihydroxypyrrolizidine-3,5-dicarboxylic acids (171a and 171b).

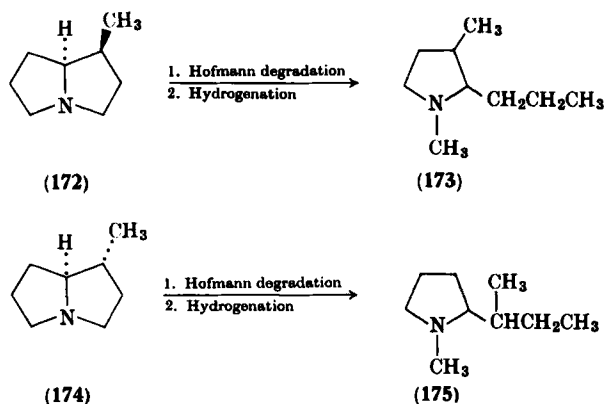
Some transformations of ethyl 3-oxopyrrolizidine-5-acetate were described in the same communication (hydrogenation of unsaturated 3-oxopyrrolizidines, see ref. 116a).

^{116a} V. Carelli, M. Cardellini, and F. Morlacchi, *Ann. Chim. (Rome)* **51**, 591, 604 (1961).



F. PYRROLIZIDINE RING CLEAVAGE

This group of reactions includes the Hofmann degradation of the heterocyclic rings of heliotridane and pseudoheliotridane, which was used in the course of their structural analysis; the ozonolysis of isoheliotridene (see Section III, B); and the degradation of 3,5-dioxopyrrolizidine by nucleophilic reagents. The direction of the Hofmann degradation of 1-methylpyrrolizidine depends upon its configuration.^{86, 100} Thus, heliotridane (172), when subjected to Hofmann degradation and subsequent hydrogenation of the unsaturated compound obtained, afforded 1,3-dimethyl-2-propylpyrrolidine (173); the structure of the pyrrolidine was finally confirmed by synthesis.¹¹⁷ However, analogous reactions with pseudoheliotridane (174) led to *N*-methyl-2-*sec*-butylpyrrolidine (175).

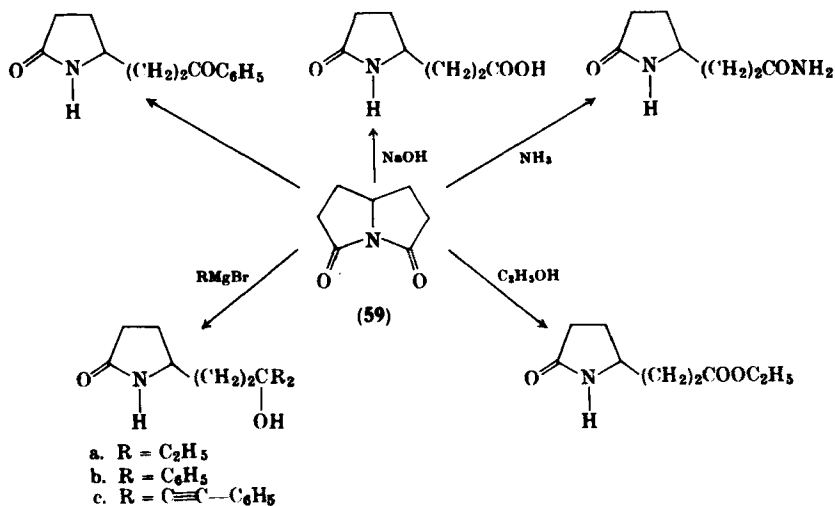


Micheel and Flitsch^{116, 118} used 3,5-dioxopyrrolizidine (59) and 3-(ethoxycarbonylmethylene)pyrrolizid-5-one (166) as starting compounds in the synthesis of various pyrrolizidine derivatives. The series

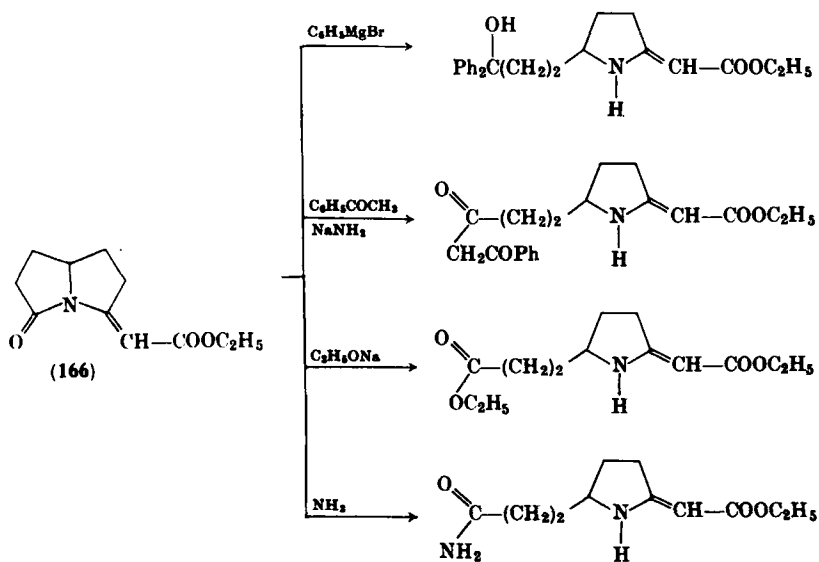
¹¹⁷ R. Adams and E. F. Rogers, *J. Am. Chem. Soc.* **63**, 228 (1941).

¹¹⁸ F. Micheel and W. Flitsch, *Chem. Ber.* **89**, 120 (1956).

of reactions shown in Scheme 8 were carried out with 3,5-dioxopyrrolizidine. Analogous transformations starting with 3-carbethoxymethylenepyrrolizid-5-one are presented in Scheme 9.



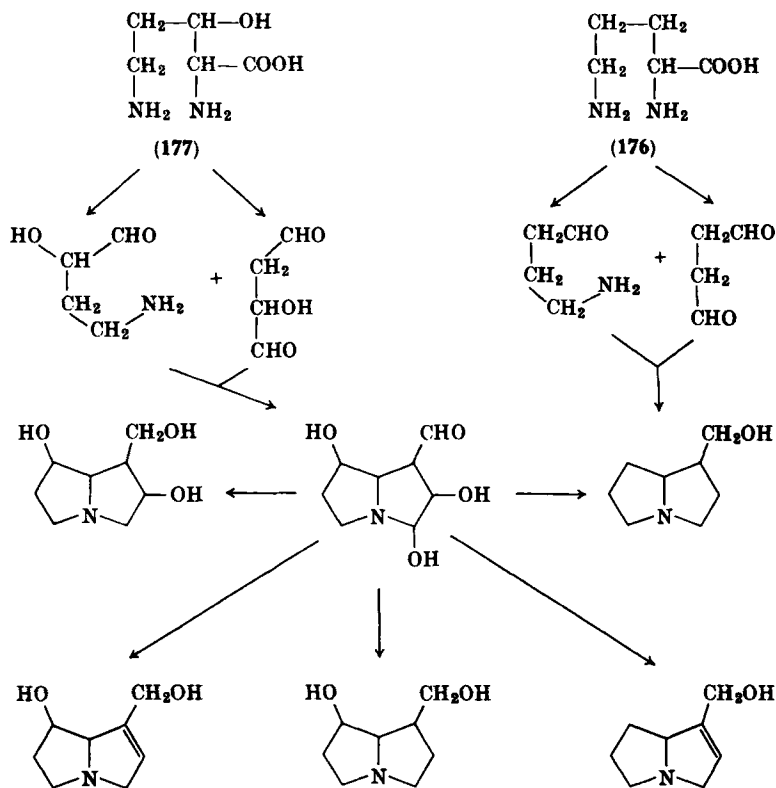
SCHEME 8



SCHEME 9

V. Biogenesis of Naturally Occurring Pyrrolizidines

Biogenetic pathways leading to naturally occurring pyrrolizidine bases were proposed by Robinson, Schöpf, and Lukeš (see, e.g., refs. 119–121) in their publications concerned with the biogenesis of alkaloids. The most probable precursors of the pyrrolizidine system are commonly accepted to be ornithine (176), hydroxyornithine (177), and their biogenetic equivalents. It is noteworthy that (\pm) - β -hydroxy-*N*-methylnorvaline (178) (structurally related to ornithine) was isolated



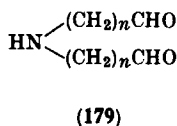
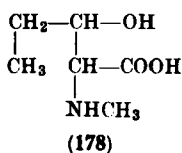
SCHEME 10

¹¹⁹ R. Robinson, "The Structural Relations of Natural Products," p. 72. Oxford Press, London, 1955.

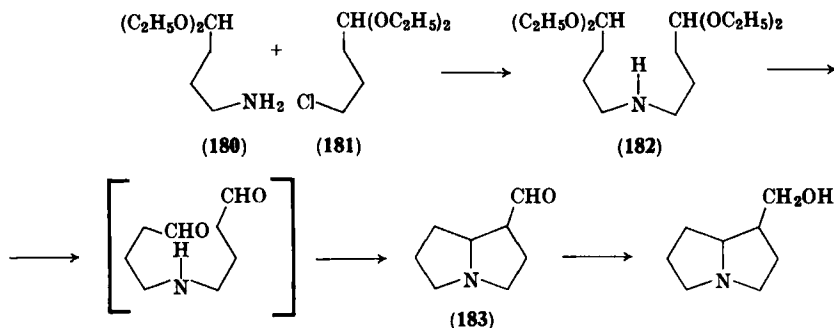
¹²⁰ C. Schöpf, *Angew. Chem.* **61**, 32 (1949).

¹²¹ R. Lukeš, *Chem. Zvesti* **5**, 51 (1951).

from *Crotalaria juncea*, together with pyrrolizidine alkaloids.¹²² The biogenetic pathways proposed by these authors are presented in Scheme 10. The hypothesis involves the assumption that the iminoaldehydes (179) are intermediates in the biosynthesis of 1-hydroxymethylpyrrolizidines and related heterocyclic systems.¹²⁰ In accord with this viewpoint, 1-hydroxymethylpyrrolizidine has been (chemi-



cally) synthesized *in vitro* from di-(4-oxo-*n*-butyl)amine under physiological conditions^{109, 123} (cf. refs. 124 and 125).



The bis-diethylacetal of di-(4-oxo-*n*-butyl)amine (182) was obtained from γ -aminobutyraldehyde diethylacetal (180) and γ -chlorobutyraldehyde acetal (181) and, after removal of acetal protecting groups, converted into 1-formylpyrrolizidine (183) without isolation of the intermediates. The final condensation was achieved by Babor *et al.*,¹⁰⁹ who isolated 1-formylpyrrolizidine in *ca.* 10–15% yield at pH 4–4.5. Hydrogenation of the compound over platinum afforded 1-hydroxymethylpyrrolizidine, which they claimed to be (\pm)-isoretronecanol. Leonard and Blum¹²³ carried out the same condensation at pH 7 and reduced the resultant aldehyde, without isolation, with sodium boro-

¹²² R. Adams and M. Gianturco, *J. Am. Chem. Soc.* **78**, 1919 (1956).

¹²³ N. J. Leonard and S. Blum, *J. Am. Chem. Soc.* **82**, 502 (1960).

¹²⁴ E. E. van Tamelen and R. L. Foltz, *J. Am. Chem. Soc.* **82**, 502 (1960).

¹²⁵ K. Winterfeld and R. Knieps, *Arch. Pharm.* **293**, 65, 325 (1960).

hydride to 1-hydroxymethylpyrrolizidine; the latter compound was isolated as 1-benzoyloxymethylpyrrolizidine in ca. 50% yield. According to Leonard and Blum, the amino-alcohol is (\pm)-trachelanthamidine. The synthesis is an excellent illustration of the possible biogenetic importance of di-(4-oxo-*n*-butyl)amine, however the stereochemistry of the condensation needs to be investigated further.

Author Index

Numbers in parentheses are reference numbers and indicate that an author's work is referred to although his name is not cited in the text.

A

Aasa, R., 220
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